

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE  
ANESTHETIC AND ANALGESIC DRUG PRODUCTS  
ADVISORY COMMITTEE (AADPAC) AND THE  
DRUG SAFETY AND RISK MANAGEMENT  
ADVISORY COMMITTEE (DSaRM)

Tuesday, June 26, 2018

9:30 a.m. to 4:22 p.m.

Open Session

DoubleTree by Hilton Hotel Bethesda

Washington DC, Grand Ballroom

8120 Wisconsin Avenue

Bethesda, Maryland

1 **Meeting Roster**

2 **ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Yinghua S. Wang, PharmD, MPH**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7 ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY

8 COMMITTEE MEMBERS

9 (Voting)

10  
11 **Raeford E. Brown, Jr., MD, FAAP** (via telephone)

12 Professor of Anesthesiology and Pediatrics

13 College of Medicine

14 University of Kentucky

15 Lexington, Kentucky

16

17

18

19

20

21

22

1 Basavana G. Goudra, MD, FRCA, FCARSCI

2 Clinical Associate Professor of Anesthesiology and

3 Critical Care Medicine

4 Director of Endoscopy Anesthesia Services at the

5 Penn Presbyterian Medical Center

6 Perelman School of Medicine

7 Hospital of the University of Pennsylvania

8 Philadelphia, Pennsylvania

9  
10 Mary Ellen McCann, MD, MPH

11 *(Acting Chairperson)*

12 Associate Professor of Anesthesia

13 Harvard Medical School

14 Senior Associate in Anesthesia

15 Boston Children's Hospital

16 Boston, Massachusetts

17  
18 Abigail B. Shoben, PhD

19 Associate Professor, Division of Biostatistics

20 College of Public Health

21 The Ohio State University

22 Columbus, Ohio

1        Lonnie Zeltzer, MD  
2        Director, Pediatric Pain and Palliative Care  
3        Program  
4        Division of Pediatric Hematology-Oncology  
5        Distinguished Professor of Pediatrics,  
6        Anesthesiology, Psychiatry and Biobehavioral  
7        Sciences  
8        David Geffen School of Medicine  
9        Los Angeles, California  
10  
11       ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY  
12       COMMITTEE MEMBER (Non-Voting)  
13       W. Joseph Herring, MD, PhD  
14       (*Industry Representative*)  
15       Associate Vice President  
16       Clinical Neuroscience  
17       Merck Research Laboratories  
18       North Wales, Pennsylvania  
19  
20  
21  
22

1 DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

2 MEMBERS (Voting)

3 Marie R. Griffin, MD, MPH

4 Professor, Health Policy and Medicine

5 Director, Vanderbilt MPH Program

6 Department of Health Policy

7 Vanderbilt University Medical Center

8 Nashville, Tennessee

9  
10 Steven B. Meisel, PharmD, CPPS

11 System Director of Medication Safety

12 Fairview Health Services/HealthEast Care System

13 Minneapolis, Minnesota

14  
15 Suzanne B. Robotti

16 *(Consumer Representative)*

17 Executive Director

18 DES Action USA

19 Founder and President

20 MedShadow Foundation

21 New York, New York

22

1       **TEMPORARY MEMBERS (Voting)**

2       **Cynthia L. Arfken PhD**

3       **Professor**

4       **Department of Psychiatry and Behavioral**

5       **Neurosciences**

6       **Wayne State University School of Medicine**

7       **Detroit, Michigan**

8

9       **Jeffrey Brent, MD, PhD**

10       **Distinguished Clinical Professor of Medicine**

11       **University of Colorado School of Medicine**

12       **Aurora, Colorado**

13

14       **Daniel Ciccarone, MD, MPH**

15       **Professor**

16       **Family and Community Medicine**

17       **University of California San Francisco**

18       **San Francisco, California**

19

20

21

22

1     John B. Hertig, PharmD, MS, CPPS

2     Associate Director

3     Center for Medication Safety Advancement

4     College of Pharmacy, Purdue University

5     Indianapolis, Indiana

6  
7     Lewis S. Nelson, MD

8     Professor and Chair

9     Department of Emergency Medicine

10    Director, Division of Medical Toxicology

11    Chief of Service, Emergency Department

12    University Hospital

13    Rutgers New Jersey Medical School

14    Newark, New Jersey

15  
16    Thomas E. Prisinzano, PhD

17    Professor, Department of Medicinal Chemistry

18    School of Pharmacy

19    University of Kansas

20    Lawrence, Kansas

21

22

1 Jennifer M. Spotila, JD

2 (Patient Representative)

3 Philadelphia, Pennsylvania

4  
5 Gregory Terman, MD, PhD

6 Professor, Department of Anesthesiology and

7 Pain Medicine and the Graduate Program

8 in Neuroscience

9 Director, University of Washington Medical Center

10 Acute Pain Service

11 University of Washington

12 Seattle, Washington

13  
14 Jon E. Zibbell, PhD

15 Senior Public Health Scientist

16 RTI International

17 Atlanta, Georgia

18

19

20

21

22

1 FDA PARTICIPANTS (Non-Voting)

2 Sharon Hertz, MD

3 Director

4 Division of Anesthesia, Analgesia and Addiction

5 Products (DAAAP)

6 Office of Drug Evaluation II (ODE-II)

7 Office of New Drugs (OND), CDER, FDA

8

9 Judy Staffa, PhD, RPh

10 Associate Director for Public Health Initiatives

11 Division of Epidemiology II (DEPI-II)

12 Office of Pharmacovigilance and Epidemiology

13 (OPE)

14 Office of Surveillance and Epidemiology (OSE)

15 CDER, FDA

16

17 Lisa Wiltrout, MD

18 Medical Officer

19 DAAAP, ODE-II, OND, CDER, FDA

20

21

22

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Mary Ellen McCann, MD, MPH	12
5	Conflict of Interest Statement	
6	Yinghua Wang, PharmD	17
7	FDA Introductory Remarks	
8	Sharon Hertz, MD	21
9	<b>Applicant Presentations - Pain Therapeutics</b>	
10	Introduction	
11	Remi Barbier	32
12	In Vitro Abuse Deterrence	
13	Michael Crowley, PhD	37
14	In Vivo Abuse Deterrence	
15	Lynn Webster, MD	52
16	Clinical Development	
17	Nadav Friedmann, PhD, MD	61
18	Excipient Safety	
19	Stephen Montgomery, PhD	65
20	Risk Management and Conclusion	
21	Michael Marsman, PharmD	70
22		

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Clarifying Questions	73
4	<b>FDA Presentations</b>	
5	Category 3 Oral Study and Category 1	
6	Smoking Study	
7	James Tolliver, PhD	86
8	Review of Recent Epidemiologic Data on	
9	Use Misuse and Abuse of Oxycodone	
10	Mallika Mundkur, MD, MPH	95
11	Remoxy ER: Multidisciplinary Review	
12	Lisa Wiltrout, MD	112
13	Clarifying Questions	122
14	Open Public Hearing	147
15	Clarifying Questions (continued)	180
16	Charge to the Committee	195
17	Questions to the Committee and Discussion	200
18	Adjournment	267
19		
20		
21		
22		

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

2                   (9:30 a.m.)

3                   **Call to Order**

4                   **Introduction of Committee**

5                   DR. McCANN: Good morning, everybody. I  
6 would first like to remind everyone to please  
7 silence your cell phones, smartphones, and any  
8 devices if you've not already done so. I would also  
9 like to identify the FDA press contact, Jennifer  
10 Dooren. If you are present, please stand. Thank  
11 you.

12                   My name is Mary Ellen McCann, and I am the  
13 acting chairperson of the Anesthetic and Analgesic  
14 Drug Products Advisory Committee, and I will be  
15 chairing this meeting. I will now call the joint  
16 meeting of the Anesthetic and Analgesic Drug  
17 Products Advisory Committee and the Drug Safety and  
18 Risk Management Advisory  
19 Committee to order. We will start by going around  
20 the table and introducing ourselves. We will start  
21 with the FDA on my left and go around the table.

22                   DR. HERTZ: Good morning. I'm Sharon. I am

1 the division director for the Division of  
2 Anesthesia, Analgesia, and Addiction Products.

3 DR. STAFFA: Good morning. I'm Judy Staffa.  
4 I'm with the Office of Surveillance and  
5 Epidemiology at the Center for Drugs, FDA.

6 DR. WILTROUT: Good morning. I'm Lisa  
7 Wilttrout. I'm a medical officer in the Division of  
8 Anesthesia, Analgesia, and Addiction Products.

9 DR. HERTIG: Good morning. John Hertig with  
10 Purdue University, their Center for Medication and  
11 Safety Advancement in Indianapolis, Indiana.

12 DR. BRENT: Good morning, everybody. My  
13 name is Jeffrey Brent. I'm a medical toxicologist  
14 and distinguished professor of medicine at the  
15 University of Colorado School of medicine.

16 DR. TERMAN: I'm Greg Terman, professor of  
17 anesthesiology and pain medicine at the University  
18 of Washington in Seattle.

19 DR. PRISINZANO: Good morning. I'm Tom  
20 Prisinzano, professor of medicinal chemistry at the  
21 School of pharmacy at the University of Kansas.

22 DR. NELSON: Good morning. I'm Lewis

1 Nelson. I'm a professor of emergency medicine and  
2 medical toxicologist at Rutgers New Jersey Medical  
3 School in Newark, New Jersey. And I oversee the  
4 New Jersey Poison Control center.

5 DR. MEISEL: Steve Meisel, director of  
6 medication safety for Fairview Health Services and  
7 the University of Minnesota Health System in  
8 Minneapolis.

9 DR. WANG: Yinghua Wang, designated federal  
10 officer, FDA.

11 DR. McCANN: Mary Ellen McCann. I'm a  
12 pediatric anesthesiologist and associate professor  
13 of anesthesiology at Harvard Medical School and  
14 Boston Children's Hospital.

15 MS. SPOTILA: Good morning. My name is  
16 Jennifer Spotila. I've lived with chronic pain for  
17 more than 20 years and have been on opioid  
18 treatments for more than 10.

19 MS. ROBOTTI: Hi. I'm Suzanne Robotti. I'm  
20 the founder of MedShadow Foundation and the  
21 executive director of DES Action USA.

22 DR. GRIFFIN: Good morning. I'm Marie

1 Griffin. I'm a pharmacoepidemiologist and an  
2 internist and a professor of medicine and health  
3 policy at Vanderbilt University.

4 DR. ZELTZER: Hi. I'm Lonnie Seltzer. I  
5 direct the pediatric pain and palliative care  
6 program at UCLA and distinguished professor of  
7 pediatrics, anesthesiology, and psychiatry at UCLA.

8 DR. SHO BEN: Good morning. I'm Abby Shoben.  
9 I'm an associate professor of biostatistics at the  
10 Ohio State University.

11 DR. GOUDRA: Basavana Goudra, associate  
12 professor of anesthesiology and critical care  
13 medicine at Penn Medical Center, Philadelphia.

14 DR. ZIBBELL: Good morning, everybody. I'm  
15 John Zibbell, a behavioral health scientist, RTI  
16 International, Atlanta, Georgia, and also a  
17 professor of anthropology at Emory University.

18 DR. CICCARONE: Good morning, everyone. My  
19 name is Dan Ciccarone. I'm a family medicine and  
20 addiction medicine specialist and professor of  
21 family and community medicine at University of  
22 California, San Francisco.

1 DR. ARFKEN: Good morning. My name is  
2 Cynthia Arfken. I'm an epidemiologist and  
3 professor of psychiatry and behavioral  
4 neurosciences, Wayne State University, Detroit,  
5 Michigan.

6 DR. HERRING: Hello. Good morning. I'm Joe  
7 Herring. I'm a neurologist and associate vice  
8 president of clinical neuroscience at Merck  
9 Research Laboratories and industry representative  
10 to the AADPAC committee.

11 DR. McCANN: Thank you.

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

22 In the spirit of the Federal Advisory

1 Committee Act and the Government in the Sunshine  
2 Act, we ask that the advisory committee members  
3 take care that their conversations about the topic  
4 at hand take place in the open forum of the  
5 meeting. We are aware that members of the media  
6 are anxious to speak with the FDA about these  
7 proceedings. However, FDA will refrain from  
8 discussing the details of this meeting with the  
9 media until its conclusion. Also, the committee is  
10 reminded to please refrain from discussing the  
11 meeting topic during breaks or lunch. Thank you.

12 Now I will pass it to Yinghua Wang who will  
13 read the Conflict of Interest Statement.

14 **Conflict of Interest Statement**

15 DR. WANG: The Food and Drug Administration  
16 is convening today's joint meeting of the  
17 Anesthetic and Analgesic Drug Products Advisory  
18 Committee and the Drug Safety and Risk Management  
19 Advisory Committee under the authority of the  
20 Federal Advisory Committee Act of 1972. With the  
21 exception of the industry representative, all  
22 members and temporary voting members of the

1 committees are special government employees or  
2 regular federal employees from other agencies and  
3 are subject to federal conflict of interest laws  
4 and regulations.

5 The following information on the status of  
6 these committees' compliance with the federal  
7 ethics and conflict of interest laws, covered by  
8 but not limited to those found at 18 USC, Section  
9 208, is being provided to participants in today's  
10 meeting and to the public. FDA has determined that  
11 members and temporary voting members of these  
12 committees are in compliance with federal ethics  
13 and conflict of interest laws.

14 Under 18 USC, Section 208, Congress has  
15 authorized FDA to grant waivers to special  
16 government employees and regular federal employees  
17 who have potential financial conflicts when it is  
18 determined that the agency's need for a special  
19 government employee's service outweighs his or her  
20 potential financial conflict of interest or when  
21 the interest of a regular federal employee is not  
22 so substantial as to be deemed likely to affect the

1 integrity of the services which the government may  
2 expect from the employee.

3           Related to the discussions of today's  
4 meeting, members and temporary voting members of  
5 these committees have been screened for potential  
6 financial conflicts of interests of their own, as  
7 well as those imputed to them, including those of  
8 their spouses and minor children, and for purposes  
9 of 18 USC, Section 208, their employers. These  
10 interests may include investments, consulting,  
11 expert witness testimony, contracts, grants,  
12 CRADAs, teaching, speaking, writing, patents and  
13 royalties, and primary employment.

14           Today's agenda involves discussion of new  
15 drug application 022324, oxycodone extended-release  
16 capsules submitted by Pain Therapeutics with the  
17 proposed indication of the management of pain  
18 severe enough to require daily, around-the-clock,  
19 long-term opioid treatment and for which  
20 alternative treatment options are inadequate. The  
21 product is intended to have abuse-deterrent  
22 properties based on its physicochemical properties.

1           The committees will be asked to discuss  
2 whether the data submitted by the applicant are  
3 sufficient to support labeling of the product with  
4 the properties expected to deter abuse. This is a  
5 particular matters meeting during which specific  
6 matters related to Pain Therapeutics' NDA will be  
7 discussed.

8           Based on the agenda for today's meeting and  
9 all financial interests reported by the committee  
10 members and temporary voting members, no conflict  
11 of interest waivers have been issued in connection  
12 with this meeting. To ensure transparency, we  
13 encourage all standing committee members and  
14 temporary voting members to disclose any public  
15 statements that they have made concerning the  
16 product at issue.

17           With respect to FDA's invited industry  
18 representative, we would like to disclose that Dr.  
19 William Herring is participating in this meeting as  
20 a nonvoting industry representative acting on  
21 behalf of regulated industry. Dr. Herring's role  
22 at this meeting is to represent industry in general

1 and not any particular company. Dr. Herring is  
2 employed by Merck and Company.

3 We would like to remind members and  
4 temporary voting members that if the discussion  
5 involves any other products or firms not already on  
6 the agenda for which an FDA participant has a  
7 personal and imputed financial interest, the  
8 participants need to exclude themselves from such  
9 involvement, and their exclusion will be noted for  
10 the record. FDA encourages all other participants  
11 to advise the committee of any financial  
12 relationships that they may have with the firm at  
13 issue. Thank you.

14 DR. McCANN: We will now proceed with the  
15 FDA's introductory remarks from Dr. Sharon Hertz.

16 **FDA Introductory Remarks**

17 DR. HERTZ: Good morning, Dr. McCann,  
18 members of the DSaRM, Drug Safety and Risk  
19 Management Advisory Committee -- sorry about  
20 that -- and the Anesthesia and Analgesia Drug  
21 Advisory Committee, and invited guests. Thank you  
22 all for being here for this advisory committee

1 meeting.

2           At this joint meeting, we'll be discussing  
3 this application from Pain Therapeutics for this  
4 new extended-release intended abuse-deterrent  
5 oxycodone product. It's intended to deter abuse by  
6 the oral, nasal, intravenous, and inhalation route.  
7 The relevant indication would be management of pain  
8 severe enough to require daily, around-the-clock,  
9 long-term opioid treatment and for which  
10 alternative options are inadequate. This is  
11 generally the indication that we use for opioid  
12 products that are appropriate for chronic pain  
13 management.

14           We have heard concerns at a number of  
15 advisory committees and in other settings that the  
16 approval of new opioid analgesics may be a source  
17 of increase in the prescribing and availability of  
18 these products, and therefore may contribute to an  
19 increase in misuse and abuse.

20           There has been a publication, based on data  
21 reviewed by FDA, that has shown that while the  
22 number of opioid prescriptions has been decreasing

1       since 2012, there have been many approvals of new  
2       both innovative as well as generic products. So  
3       there really is not a correlation with new drug  
4       approvals and an increase in prescribing. So as  
5       you think about the meeting today, know that we're  
6       keeping an eye on that, but that doesn't seem to be  
7       a problem.

8               Over the years, we've gained a lot of  
9       knowledge and experience reviewing abuse-deterrent  
10       formulations. We've approved 10 opioid analgesics  
11       with labeling consistent with our guidance on the  
12       development of abuse-deterrent opioid analgesics,  
13       and these have included extended-release products  
14       and one immediate-release product. A number of  
15       these products have never been marketed for reasons  
16       that one would need to ask the applicants: five of  
17       the approved ADFs or oxycodone products for  
18       extended release, two of which have not been  
19       marketed, and one immediate release.

20               The goal, based on our guidance, is to  
21       evaluate relevant routes of administration or  
22       routes of abuse and to use a step-wise approach to

1 gather data, and ultimately to have postmarketing  
2 data supporting premarketing evaluations. As you  
3 are all I'm sure quite familiar, the category 1  
4 testing is in vitro testing on methods of  
5 manipulation.

6 The category 2 is pharmacokinetic studies of  
7 products in the manipulated state compared to  
8 intact and other comparators. Category 3 are human  
9 abuse potential studies looking at subjective  
10 effects with appropriate controls in the context of  
11 manipulated and unmanipulated product. And then  
12 category 4 is postmarketing data that supports the  
13 conclusions from the premarketing data.

14 When we write labeling for these, we say  
15 that these findings can lead one to expect that  
16 there would be a reduction in abuse by virtue of  
17 the methods of manipulation that any given  
18 formulation can make more difficult. Note, I  
19 didn't say prevent abuse, nor did I mention the  
20 word "addiction." I'll come back to that in a  
21 second.

22 With the goal of category 4 data providing

1 support for the premarketing studies, we're really  
2 hoping to get that information to be able to both  
3 inform the labeling of products, but also to inform  
4 the wider community. Although there have been many  
5 publications describing potential benefits for some  
6 abuse-deterrent opioid products on the market, we  
7 at FDA have not been asked to review data to add  
8 postmarketing information to labeling by any of the  
9 companies with currently marketed products who may  
10 have some amount of data, and that always makes me  
11 wonder why we do examine data quite closely.

12 So at this point in time, based on the  
13 information available to us, the literature, what  
14 we've come to learn over time, it's reasonable to  
15 conclude that the utility of abuse-deterrent opioid  
16 analgesics has yet to be determined in the real  
17 world. Challenges to determining the impact of  
18 abuse-deterrent analgesics include difficulty  
19 measuring the important outcomes, abuse, misuse,  
20 overdose, and death, and then attribute any changes  
21 that are found to specific actions such as the  
22 formulation, because we have to remember that there

1 are numerous ongoing federal, state, and local  
2 activities intended to address the problem of  
3 prescription opioid abuse.

4 So it's necessary to look at the outcomes  
5 for any one product in the context of what is  
6 happening with other similar products or prior  
7 non-abuse-deterrent product. Some review articles  
8 describe decreases in abuse of a particular  
9 abuse-deterrent product following its marketing,  
10 but also generally describe a contemporaneous  
11 increase in the rate of abuse of other prescription  
12 opioids or illicit drugs during the same periods  
13 examined.

14 So far, many articles have concluded that  
15 there's not been an overall net positive effect of  
16 reduced abuse across the community, but perhaps  
17 more shift. One downside of the abuse-deterrent  
18 products that has emerged is a possible false sense  
19 of safety because of a misunderstanding on the part  
20 of some prescribers that these products are less  
21 addictive or cannot be abused, as they fail to  
22 understand what the limitations of abuse-deterrent

1 properties are, that they make a product more  
2 difficult to manipulate for the purpose of abuse or  
3 potentially making a product less reinforcing  
4 following manipulation for abuse.

5 As these are all analgesic products, all  
6 must be able to deliver the opioid to the patient,  
7 so they all remain abusable by the oral route in  
8 the original unmanipulated state. As opioids,  
9 these products all remain potentially addictive,  
10 and none of the reformulations into abuse-deterrent  
11 products has resulted in a change in scheduling.  
12 They all remain in the same original schedule as  
13 non-abuse-deterrent products.

14 In addition to the limitations in what an  
15 abuse-deterrent formulation can accomplish, there  
16 is the concern about unintended consequences.  
17 Patients early on had some problems with ADF  
18 products sticking to mucosal surfaces -- for  
19 instance, the esophagus -- at times requiring even  
20 endoscopic removal or surgery.

21 With Opana ER, which we brought to advisory  
22 committee last year, there were a number of

1 findings that were disturbing, leading to us  
2 requesting that it be removed from market:  
3 outbreaks of HIV and hep C infections because new  
4 methods for manipulation for IV abuse led to more  
5 needle sharing as well as microangiopathic  
6 thrombocytopenia related to excipients intended to  
7 impart abuse-deterrent properties, and effects of  
8 other methods developed to support intravenous  
9 abuse of that product. In addition, there were  
10 data suggesting a shift from nasal to the more  
11 dangerous IV route of abuse.

12 Not all ADFs have met the hoped for outcomes  
13 when studied. We have determined that when a  
14 product that can reasonably be expected to have  
15 abuse-deterrent properties, based on the  
16 formulation and studies conducted, fails to  
17 demonstrate those properties and preapproval  
18 studies, it's important for prescribers to  
19 understand this information, that the product fail  
20 to meet the stated goals so they can make informed  
21 decision about the role of the product in their  
22 practice of pain management.

1           There is one product that's been approved  
2 intended to be abuse deterrent, Apadaz, which is a  
3 benzhydrocodone/acetaminophen immediate-release  
4 product that, as with all these products, has been  
5 brought before these committees and failed to meet  
6 any of the usual endpoints that are considered  
7 relevant for the premarketing support for a  
8 potential abuse-deterrent effect.

9           There was some small early changes relative  
10 to controls that we did put in labeling that's  
11 information. we don't know that there's any  
12 clinical relevance. And in all the products that  
13 we have that have had more substantive changes in  
14 the premarketing studies, we've still yet to see  
15 the hoped for public health benefits.

16           We're still waiting for that data, trying to  
17 see if these products are having the intended  
18 value. So the labeling for that product includes  
19 language describing the results of these additional  
20 secondary endpoints that are not described in our  
21 guidance and for which the clinical significance is  
22 unknown.

1           The results of this applicant's clinical  
2 trial data in vitro physical and chemical  
3 manipulation assessments and in vivo human abuse  
4 potential studies will be presented during this  
5 meeting. You'll hear presentations from the  
6 applicant and from the agency, including results  
7 from agency chemists.

8           Now, what folks may not know is that our  
9 labs have been working on studying the properties  
10 of abuse-deterrent formulations for a long time  
11 now. Sometimes our results match  
12 sponsors/applicants and sometimes they don't.  
13 That's not an indicator of any impropriety in any  
14 way.

15           The methods for evaluating these products in  
16 vitro have not been standardized, so even if  
17 similar conditions are used, in the absence of  
18 well-established standardized methods, differences  
19 happen. And you're going to hear about some  
20 differences from our lab compared to the sponsor,  
21 but I just want to make sure that it doesn't come  
22 with a particular or even implied negative intent

1 or concept, that it's just a different finding in  
2 different hands.

3 We're going to ask you if the applicant has  
4 provided adequate support for the safety and  
5 efficacy in the intended population; for the  
6 labeling, whether the labeling should include  
7 abuse-deterrent properties, and if so, which ones;  
8 and overall if the product's benefits outweigh its  
9 risks.

10 Your advice and recommendations are  
11 essential in assisting us with addressing these  
12 complex and critical public health concerns  
13 associated with these products with this whole area  
14 of therapeutics, and we're grateful that you have  
15 agreed to join us for this meeting. Thank you.

16 DR. McCANN: Thank you.

17 Both the Food and Drug Administration and  
18 the public believe in a transparent process for  
19 information-gathering and decision-making. To  
20 ensure such transparency at the advisory committee  
21 meeting, FDA believes that it is important to  
22 understand the context of an individual's

1 presentation. For this reason, FDA encourages all  
2 participants, including the applicant's nonemployee  
3 presenters, to advise the committee of any  
4 financial relationships that they may have with the  
5 applicant such as consulting fees, travel expenses,  
6 honoraria, or interest in a sponsor, including  
7 equity interest and those based upon the outcome of  
8 the meeting.

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

16 We will now proceed with Pain Therapeutics'  
17 presentations.

18 **Applicant Presentation - Remi Barbier**

19 MR. BARBIER: Good morning, and welcome to  
20 the open session of the advisory committee meeting  
21 for REMOXY. My name is Remi Barbier. I'm a drug  
22 developer. I have 25 years of experience in drug

1 discovery and drug development.

2 We have a relatively full agenda this  
3 morning, and I propose that we dive right in. A  
4 few brief words about us, Pain Therapeutics is the  
5 sponsor, obviously, of REMOXY. We are a research  
6 and development company based in the college town  
7 of Austin, Texas. We've been around for a little  
8 bit over 20 years, and in that time, our research  
9 focus has been primarily on diseases and disorders  
10 of the nervous system.

11 Before we actually start a couple of  
12 disclosures and disclaimers, when we use the term  
13 "abuse deterrence," we are not intending to  
14 designate a medical claim, but rather a general  
15 description of properties to address the abuse,  
16 misuse, and diversion of opioids. We don't know it  
17 all, and as with any company, we use a number of  
18 consultants. We pay these consultants.

19 So these consultants, in our case,  
20 Dr. Crowley, Dr. Webster, and Dr. Montgomery, have  
21 a financial relationship with the company in the  
22 form of professional fees, consulting fees,

1 expenses, and/or equity interest that may be  
2 perceived as a conflict of interest.

3 As we all know, REMOXY is in registration  
4 for approval as an extended-release gel formulation  
5 of oxycodone. REMOXY has properties that are  
6 expected to deter formulation abuse, therefore, we  
7 are seeking label claims against abuse by the  
8 injection, snorting, and smoking routes of abuse.  
9 Note at this time, we are not seeking a label claim  
10 against the oral route of abuse.

11 The FDA guidance document defines  
12 abuse-deterrence properties as, quote, "those  
13 properties shown to meaningfully deter abuse even  
14 if they do not fully prevent abuse." So from our  
15 point of view, the design goal of an  
16 abuse-deterrent formulation, or ADF, is a robust  
17 extended-release mechanism that resists dose  
18 dumping under conditions of abuse.

19 To state the obvious, and as Dr. Hertz has  
20 informed us, abuse deterrence is never and can  
21 never be abuse proof. We know that oxycodone can  
22 be extracted from REMOXY or any abuse-deterrent

1 formulation. The question is how much time,  
2 effort, and frustration is needed relative to a  
3 comparator drug? Let me repeat that because it's a  
4 very important concept. Abuse deterrence is never  
5 abuse proof, but the question for us is how much  
6 time, effort, and frustration is needed relative to  
7 a comparator drug?

8 We see several potential benefits of  
9 abuse-deterrent formulations, or ADFs. For the  
10 novice abusers, we believe ADFs can eliminate the  
11 quick, easy common method of formulation abuse,  
12 such as chewing or crushing. For recreational  
13 abusers, we believe ADFs can discourage abusers  
14 from transitioning to non-approved routes of  
15 administration such as snorting, smoking, or  
16 injection. For the advanced abusers, we believe  
17 ADFs can render manipulations or drug abuse more  
18 difficult, expensive, and time consuming, thus  
19 making manipulated drug products less rewarding.

20 But again, as Dr. Hertz pointed out, there  
21 are some severe limitations to ADFs. Drug abuse is  
22 a very, very complex problem, and ADFs alone will

1 not prevent prescription drug abuse. Furthermore,  
2 ADFs do not address the long-standing issues we've  
3 had with opioids such as euphoric effects,  
4 addiction, or potential for addiction I should say,  
5 tolerance, and dependence.

6 To us, the persistence of opioid abuse  
7 indicates a need for more robust abuse-deterrent  
8 formulations. When it comes to ADFs, we can never  
9 rest or be satisfied with the status quo. For  
10 example, after abuse-deterrent OxyContin reached  
11 the market, one research found, quote, "Although  
12 the reformulation produced an immediate drop in  
13 abuse rates, a definite ceiling effect appeared  
14 over time beyond which no further decrease was  
15 seen" unquote.

16 So our overall message is that ADFs can play  
17 a critical role in the fight against opioid abuse,  
18 but additional ADF solutions are needed.

19 Additional ADF solutions are needed to advance the  
20 science of abuse deterrence, to provide additional  
21 treatment options for physicians as well as for  
22 patients, but most of all to address certain

1       vulnerabilities of existing ER oxycodone products.  
2       And with that, I'd like to turn it over to  
3       Dr. Crowley for a review of our in vitro abuse  
4       deterrence.

5                   **Applicant Presentation - Michael Crowley**

6               DR. CROWLEY: Good morning. My name is  
7       Michael Crowley. I'm a consultant to Pain  
8       Therapeutics, and my background is in molecular  
9       pharmaceutics. I'll be discussing the category 1  
10      in vitro abuse-deterrent study results with you.

11              Eleven category 1 studies were conducted in  
12      accord with the FDA guidance, abuse-deterrent  
13      opioids evaluation and labeling issued in April of  
14      2015. These studies characterize the  
15      abuse-deterrent properties of REMOXY ER, including  
16      the degree of effort required to bypass or defeat  
17      those properties.

18              The studies were performed according to a  
19      protocol that was submitted to the FDA for their  
20      review prior to its execution. Input from the  
21      agency was incorporated into the study design. All  
22      studies were conducted by third-party laboratories

1 with prior experience performing category 1  
2 studies. Three or six replicates were performed  
3 for a given experiment, which is an industry  
4 standard.

5 The category 1 study methodology was based  
6 upon the physical and chemical properties of  
7 REMOXY; common methods of abuse for  
8 extended-release opioids; the FDA guidance with  
9 their input; clinical and scientific consultants;  
10 and internet sites frequented by opioid abusers.

11 The category 1 studies were extensive. More  
12 than 9,000 unique data points were generated from 5  
13 oral abuse simulations, 4 injection abuse  
14 simulations, and 2 smoking simulations. All  
15 results were reported in the REMOXY NDA. Due to  
16 time constraints today, only representative results  
17 that include worst case outcomes are being  
18 presented. As a reminder, the experimental  
19 conditions are blinded, and the codes were provided  
20 in the closed session.

21 The FDA guidance states, "Abuse deterrent  
22 properties can generally be established only

1 through comparison to another product."  
2 Accordingly, OxyContin ER, Xtampza ER, and  
3 Roxycodone IR were comparators in the category 1  
4 studies. OxyContin was commercially available for  
5 the duration of the studies. Xtampza was approved  
6 and commercially available later and was included  
7 in a smaller subset of the studies. Both intact  
8 and manipulated product states were evaluated.

9 REMOXY's abuse-deterrent properties were  
10 evaluated in a comprehensive battery of these  
11 studies. The studies were conducted with  
12 scientific rigor in which a physical manipulation  
13 was followed by a chemical extraction. The  
14 manipulations included simple methods using common  
15 household tools, a few procedural steps, and  
16 progressed and evolved to more complex processes  
17 using sophisticated tools, the application of  
18 stress conditions, and multiple procedural steps  
19 that require more time and effort. Extractions  
20 considered the pH, polarity, and ionic strength of  
21 the solvent. The solvent volume, agitation method,  
22 extraction temperature, and extraction time were

1 additional experimental parameters.

2           These studies simulated both intentional  
3 abuse and unintentional or accidental misuse. In  
4 some cases, the simulations required more time,  
5 expertise, equipment, and effort than a casual  
6 abuser might employ. Manipulations were directed  
7 to common routes of abuse. Oral studies evaluated  
8 the impact of tools and manipulation methodology on  
9 drug extraction at volume D.

10           Injection abuse simulations assessed  
11 syringeability and injectability, or the ability to  
12 draw the REMOXY formulation into a syringe through  
13 a needle and eject it from a syringe through a  
14 needle. In addition, injection-abuse simulations  
15 evaluated the impact of tools and manipulation on  
16 drug extraction at volumes A, B, and C. Nasal  
17 abuse simulations attempted to solidify REMOXY into  
18 a format suitable for snorting. And finally,  
19 smoking simulations measure the amount of oxycodone  
20 vaporized under heating.

21           Within a given experiment, 7 parameters were  
22 varied. REMOXY's abuse-deterrent properties were

1 evaluated using 12 manipulation methods, 24 tools,  
2 and 3 stress conditions. The extractions utilize  
3 24 solvents, 4 different volumes, 4 different  
4 agitation methods, and 4 different extraction  
5 temperatures. This represents a total of 75  
6 variables. As directed in the guidance, REMOXY was  
7 tested to failure to read. To reiterate Remi,  
8 abuse deterrence does not mean abuse proof.

9 REMOXY has unique physical and chemical  
10 properties. The high viscosity gel formulation  
11 does not flow, making it difficult to snort,  
12 syringe, or inject. In addition, the REMOXY  
13 formulation is sticky and adhesive. An abuser  
14 faces practical difficulties handling the sticky,  
15 high viscosity formulation. Manipulation methods  
16 RM2 and 8, for example, result in about a  
17 25 percent loss of the REMOXY mass before an  
18 extraction attempt can even begin.

19 When subjected to extreme heat, oxycodone  
20 degrades and an excipient boils. It releases  
21 acetic acid or vinegar, and its vapors are  
22 irritating. Later, Dr. Montgomery will be speaking

1 with you about the safety of inhaling this  
2 material. Low oxycodone extraction from REMOXY  
3 after a manipulation and extraction is intended to  
4 contribute to its abuse deterrence.

5 As we mentioned, REMOXY is highly viscous.  
6 To provide you with a frame of reference, it's  
7 about 500 times more viscous than motor oil and  
8 about 4 times more viscous than Vaseline. The  
9 REMOXY formulation is also hydrophobic and does not  
10 dissolve in aqueous-based solvents. A common and  
11 simple method of abuse involves placing an intact  
12 extended-release opioid in a liquid, waiting for it  
13 to dissolve, followed by oral ingestion.

14 Here we present extraction results from  
15 intact REMOXY after soaking in 4 solvents at volume  
16 D and temperature B using mixing type A for time 0.  
17 As you can see, 7 percent of the oxycodone dose was  
18 extracted in insolvent S1 and 49 percent of the  
19 dose was extracted in solvent S5.

20 Now, let's take a look at a oral abuse  
21 simulation in which the formulation was  
22 manipulated, followed by an extraction. In this

1 oral abuse simulation, we present the oxycodone  
2 extraction profile from manipulative REMOXY in  
3 solvent S1 at volume D and temperature B through  
4 time K. REMOXY was manipulated using 7 different  
5 methods coded RM1 through 9. Methods 8 and 9 also  
6 had stress be applied prior to the extraction. The  
7 intact, non-manipulated REMOXY extraction profile  
8 is represented by the dashed green line. As you  
9 can see, REMOXY maintained its extended-release  
10 characteristics following all 9 manipulations in  
11 solvent S1.

12 The extraction profiles of the comparator  
13 products are now illustrated. OxyContin ER intact  
14 is the dashed red line, and as you can see, there  
15 is little difference between intact OxyContin and  
16 manipulated REMOXY. OxyContin manipulated using  
17 method OM1 is a solid red line, where REMOXY, the  
18 immediate-release comparator, is the blue line.

19 OxyContin, manipulated using method 1,  
20 rapidly defeated its abuse-deterrent properties in  
21 which over 80 percent of the dose was extracted by  
22 the first time point. I want to point out that the

1 color scheme presented on this slide will be  
2 maintained going forward.

3 Solvent S5 was the most effective solvent in  
4 its class. As previous, this is the oxycodone  
5 extraction profile from manipulated REMOXY through  
6 time K at volume D and temperature B. Oxycodone  
7 extraction from REMOXY was dependent upon the  
8 manipulation method. Method 8 with stress B was  
9 the most effective method, while method 1 was the  
10 least effective method. Manipulated REMOXY  
11 maintained rate control through time K, following  
12 all 9 manipulations. By comparison, greater than  
13 80 percent of the oxycodone was extracted from  
14 manipulated OxyContin and Roxicodone by the first  
15 time point.

16 As directed in the FDA guidance, REMOXY was  
17 tested to failure. Method 10 was the most  
18 effective manipulation method to defeat REMOXY's  
19 abuse-deterrent properties. This is a  
20 sophisticated manipulation procedure requiring the  
21 use of multiple tools and 6 steps. Method 10 must  
22 be performed in a certain and specific order in

1 order to defeat REMOXY. In solvents 1 through 5,  
2 REMOXY retained rate control for time J in 3 of  
3 those 5 solvents. By comparison, under similar  
4 conditions, OxyContin retained rate control in only  
5 1.

6 Here are the results comparing oxycodone  
7 extraction from REMOXY, following manipulation  
8 methods 9 and 10 in solvent 1 at volume D. The  
9 table at the top was performed at extraction  
10 temperature B, and the table at the bottom was  
11 performed at temperature F. REMOXY's abuse of  
12 deterrent properties were defeated by method 10,  
13 which requires the use of tool 16 and  
14 6 applications of tool 12. Again, it's a  
15 complicated and sophisticated procedure, requiring  
16 6 steps in a certain order.

17 Now, let's look at extraction results from  
18 manipulated REMOXY in a different class of  
19 solvents. This figure summarizes and compares  
20 extraction results in 11 solvents, numbers 6  
21 through 16. Of these 11 solvents, only one was  
22 capable of extracting 75 percent of the oxycodone

1 dose from REMOXY, while 7 solvents extracted 75  
2 percent or more from OxyContin at time D.

3 Similarly, at time J and K, fewer solvents were  
4 capable of extracting greater than 75 percent of  
5 the dose from REMOXY compared to OxyContin.

6 REMOXY's high viscosity formulation cannot  
7 be snorted like a powder. stress condition A with  
8 manipulation methods 4, 5, and 6 failed to convert  
9 REMOXY into a form suitable for snorting. Later,  
10 Dr. Webster will report the results of a category 2  
11 and category 3 human abuse potential study in which  
12 REMOXY was applied to the nostrils of recreational  
13 opioid abusers.

14 Next, I'll discuss the results of IV abuse  
15 simulations. IV abuse simulations were performed  
16 to evaluate REMOXY's abuse-deterrent properties  
17 following manipulations and extractions and  
18 volumes A, B, and C. IV abuse simulations were  
19 conducted at temperature B through temperature F in  
20 solvents 19 through 24.

21 Here we present the extraction profile of  
22 REMOXY following manipulation using method 2 and

1 11, and in combination with stress B. The study  
2 conditions were temperature B and volume C in  
3 solvent 19. REMOXY resisted extraction following  
4 these manipulations and extraction conditions with  
5 less than 20 percent of the dose extracted by  
6 time H. In addition, application of stress B had  
7 no impact on oxycodone extraction from REMOXY.

8 Let's take a look at the comparator products  
9 and see how they fared under similar conditions.  
10 As I mentioned earlier, Xtampza was included as a  
11 comparator in a smaller subset of category 1  
12 studies. Xtampza ER is the solid purple line and  
13 was manipulated using method XM1. OxyContin is the  
14 solid red line and was manipulated using method OM2  
15 and stress B.

16 As you can see, oxycodone was rapidly  
17 extracted from OxyContin under these conditions at  
18 the very first time point. In this IV abuse  
19 simulation, REMOXY was manipulated using method 11.  
20 Stress C was applied for time D, F, and H prior to  
21 the extraction. The study conditions were  
22 solvent 24 at temperature D and volume B. So in

1 addition to a different solvent and different  
2 stress condition, this extraction was performed at  
3 a different temperature and a different volume  
4 compared to the prior slide.

5 REMOXY resisted extraction following these  
6 manipulations and extraction conditions with less  
7 than 40 percent of the dose extracted by time H.  
8 In addition, the application of stress C had no  
9 impact on oxycodone extraction from REMOXY. By  
10 comparison, you can see how rapidly oxycodone was  
11 extracted from OxyContin.

12 The worst case conditions in an IV abuse  
13 simulation were in solvent 20 at temperature F and  
14 volume C. REMOXY was manipulated using methods RM2  
15 and 11 with stress condition B applied. Under  
16 these conditions, method 2 extracted about  
17 40 percent of dose in time B. About half the dose  
18 was extracted at time H following manipulation  
19 method 11. These extraction conditions defeated  
20 both manipulated OxyContin and manipulated Xtampza.  
21 Greater than 80 percent of the dose was extracted  
22 from these two products at the first time point.

1           Now, let's turn our attention to  
2 syringeability and injectability studies.  
3 Syringeability studies were undertaken to assess  
4 whether the REMOXY formulation could be drawn into  
5 a syringe through a needle. Four needle gauges  
6 were tested, and all attempts to draw the  
7 formulation into a syringe failed. An  
8 injectability study was also performed in which the  
9 REMOXY formulation was backfilled into a syringe,  
10 and 4 needle gauges were tested to see if the  
11 REMOXY formulation can be dispensed from the  
12 syringe and through a needle.

13           In addition, the injection rate and  
14 temperature were also varied. The REMOXY  
15 formulation could not be injected from a syringe  
16 under any of the conditions that were tested. On  
17 the next slide, a video will illustrate the  
18 injectability experiment.

19           (Video played.)

20           DR. CROWLEY: Please direct your attention  
21 to the red oval. The experiment was conducted  
22 using needle size d at temperature B. As you can

1 see, when the plunger rod is pressed, the REMOXY  
2 formulation backflowed around the rubber stopper  
3 rather than through the needle.

4 I realize that may be hard to see from the  
5 back.

6 Now, I'll discuss the smoking abuse  
7 simulation results. Smoking is a less common route  
8 of abuse for oxycodone due to the narrow margin  
9 between the vaporization temperature and  
10 temperature where oxycodone degrades. REMOXY was  
11 heated to temperature I, and its vapors were  
12 continuously collected. The quantity of oxycodone  
13 recovered from the vapors was determined against  
14 time. As you can see in this image, REMOXY  
15 carbonizes at this temperature. Minimal oxycodone  
16 was recovered from REMOXY vapors at time D and  
17 time F. A larger quantity of oxycodone was  
18 recovered from the vapors of OxyContin, then  
19 REMOXY, under identical experimental conditions.

20 This concludes the results of the category 1  
21 studies, which I will now summarize. The category  
22 1 studies demonstrated the physical and chemical

1 properties, the REMOXY formulation impart abuse  
2 deterrence. REMOXY provides resistance to  
3 manipulations and extraction procedures. Its high  
4 viscosity formulation sticks to tools, making it  
5 difficult to manipulate and recover the entire  
6 quantity of the mass within a capsule. The studies  
7 also demonstrate it's difficult to syringe and  
8 inject and could not be converted into a form  
9 suitable for snorting. Minimal oxycodone was  
10 recovered in smoking simulations.

11 Finally, there are no visual cues to alert  
12 an abuser that REMOXY seat might be defeated or  
13 compromised. By visual cues, I mean a solution is  
14 not formed, nor a powder formed that could be  
15 snorted. Lacking visual cues, an abuser must rely  
16 upon guesswork, trial and error, or the use of  
17 sophisticated laboratory equipment such as an HPLC.  
18 To gauge the success or failure of the various  
19 manipulation methods, an abuser would also need to  
20 record their experimental procedures, what tools  
21 they used, which solvents they used, and for how  
22 long in order to identify conditions for REMOXY

1 abuse. The complexity, frustration, and tools  
2 needed to abuse REMOXY are intended to contribute  
3 to its abuse deterrence.

4 Next, Dr. Webster will discuss the category  
5 2 and 3 in vivo abuse-deterrent studies.

6 **Applicant Presentation - Lynn Webster**

7 DR. WEBSTER: Good morning, everyone. I'm  
8 Lynn Webster, vice president of scientific affairs  
9 at PRA Health Sciences. My board certifications  
10 include anesthesia, pain medicine, and addiction  
11 medicine. As most of you know, I presented to you  
12 several times on abuse-deterrent formulations. I'm  
13 here today because I was the principal investigator  
14 of REMOXY's oral and nasal human abuse potential  
15 studies.

16 My presentation will show the results of the  
17 category 2 and category 3 assessments for both the  
18 oral and nasal abuse potential studies. The  
19 primary objective of the oral human abuse study was  
20 to compare the relative abuse potential of chewed  
21 40 milligrams REMOXY ER versus crushed  
22 40 milligrams IR oxycodone in solution.

1           The oral abuse potential study was performed  
2 prior to the FDA guidance issued in 2015. It was a  
3 single center, randomized, triple dummy,  
4 double-blind 4-way crossover design in recreational  
5 opioid abusers; 46 subjects completed the study.  
6 The study included a screening visit, the  
7 qualification phase using a naloxone challenge, a  
8 drug discrimination phase, and a treatment phase.  
9 A drug discrimination phase was used to ensure  
10 subjects could differentiate between the effects of  
11 20 and 40 milligrams IR and placebo.

12           During the treatment phase, subjects were  
13 randomized to 1 of 4 treatment sequences, 40  
14 milligrams intact REMOXY ER, 40 milligrams chewed  
15 REMOXY ER, 40 milligrams crushed oxycodone in IR in  
16 solution, and placebo. Subjects were instructed to  
17 chew up to 5 minutes. The primary objective was to  
18 compare the relative abuse potential of chewed  
19 40 milligrams REMOXY ER versus crushed  
20 40 milligrams IR oxycodone in solution.

21           The study had 4 co-primary endpoints: drug  
22 liking Emax, drug high Emax, drug liking area under

1 the effect curve zero to 2 hours, and drug high  
2 area under the effect curve zero to 2 hours. Drug  
3 liking endpoints were measured using a unipolar  
4 scale ranging from zero to 100. For example,  
5 overall drug liking was assessed by asking the  
6 subject, "Do you like the effect you are feeling  
7 now?" where a score of zero was not at all, and the  
8 score of 100 would be extremely. As per FDA  
9 guidance, data was generated for the 46 subjects  
10 who received all 4 study treatments.

11 Results of the study showed statistically  
12 significant differences between chewed REMOXY and  
13 immediate release oxycodone for 2 of the 4 primary  
14 endpoints. The two endpoints that were associated  
15 with significantly lower scores with chewed REMOXY  
16 compared to IR oxycodone were the area under the  
17 effect curve of zero to 2 hours for drug liking and  
18 drug high. However, no statistical differences  
19 were observed between drug liking and drug high  
20 Emax when comparing chewed REMOXY ER with IR  
21 oxycodone.

22 This slide shows the PK results of 40

1 milligrams of REMOXY intact, 40 milligrams of  
2 REMOXY chewed as the method of manipulation, and 40  
3 milligrams crushed IR oxycodone in solution. The  
4 mean plasma concentration of intact REMOXY ER was  
5 statistically lower than crushed IR oxycodone at  
6 each time point following drug administration  
7 through 4 hours. However, the mean plasma  
8 concentration of chewed REMOXY was statistically  
9 lower than crushed oxycodone IR at only early time  
10 points of 30 and 60 minutes.

11           When examining the overall time course,  
12 there was a statistical difference in drug liking  
13 scores between REMOXY ER manipulated and oxycodone  
14 IR at earlier time points of 30, 60, and 90 minutes  
15 but not at 2 hours. Early time course effects are  
16 important as faster onset of effect has been  
17 associated with greater drug liking overall in  
18 recreational users.

19           The same early time course differences were  
20 observed with drug high when comparing 40  
21 milligrams REMOXY chewed and 40 milligrams  
22 oxycodone IR at earlier time points of 30, 60, and

1 90 minutes, but again not at 2 hours.

2 In summary, the oral abuse potential steady  
3 met 2 of the 4 primary endpoints but did not meet  
4 the primary endpoints of drug high or drug liking  
5 Emax. At time points 30, 60, and 90 minutes,  
6 REMOXY demonstrated a statistical difference in  
7 favor of chewed REMOXY when compared to  
8 oxycodone IR crushed in solution taken orally, but  
9 there wasn't a difference at the 2 hours.

10 Now, let's look at the nasal abuse potential  
11 study. In this study, the primary objective was to  
12 compare the relative abuse potential of manipulated  
13 and intact REMOXY ER to immediate-release  
14 oxycodone. This study was conducted in 2017. A  
15 secondary objective was to compare the PK profile  
16 of REMOXY ER to crushed IR oxycodone and  
17 manipulated OxyContin ER.

18 The nasal abuse potential study was a  
19 randomized, double-blind, 4-way crossover study in  
20 recreational abusers. As is typical with these  
21 types of studies, there was a screening phase,  
22 qualification phase with a naloxone challenge, a

1 discrimination phase using 40 milligrams of oral  
2 oxycodone IR, and placebo followed by the treatment  
3 phase.

4 After the double-blind treatment phase, 20  
5 subjects entered an exploratory open-labeled PK  
6 phase with manipulated 40 milligrams OxyContin  
7 administered intranasally. In the treatment phase,  
8 subjects were randomized to either intact  
9 40 milligrams of REMOXY, 40 milligrams manipulated  
10 REMOXY, 40 milligrams crushed oxycodone IR, and  
11 placebo. Manipulation technique for intranasal  
12 administration of REMOXY ER is specified in section  
13 3 of the confidential briefing book.

14 As previously mentioned, the open extension  
15 phase also used 40 milligrams manipulated OxyContin  
16 taken intranasally. As per FDA guidance, the  
17 primary endpoint was drug liking Emax comparing  
18 REMOXY ER to immediate-release oxycodone. A  
19 bipolar scale was used to evaluate drug liking PD  
20 endpoints where zero was strong disliking and 100  
21 was strong liking, and a score of 50 was neither  
22 like nor dislike.

1           The statistical analysis plan was  
2           prespecified and reviewed by the FDA. Data were  
3           generated for 36 completers from the blinded  
4           portion of the study and 20 completers from the  
5           open labeled portion.

6           The PK results of intranasally administered  
7           drugs are illustrated in this figure. Both intact  
8           and manipulated REMOXY ER demonstrated an  
9           extended-release profile and lower bioavailability  
10          than ground oxycodone IR and manipulated OxyContin  
11          IR. Cmax for manipulated and intact REMOXY was  
12          significantly lower than for ground oxycodone IR  
13          and manipulated OxyContin ER.

14          This figure shows Cmax for manipulated and  
15          intact REMOXY was significantly lower than for  
16          crushed oxycodone IR and manipulated OxyContin ER  
17          when administered intranasally. The Tmax of  
18          manipulated and intact REMOXY was also  
19          statistically longer when compared to crushed  
20          oxycodone IR and manipulated OxyContin ER. As you  
21          know, the longer Tmax or time to Cmax is generally  
22          associated with more abuse deterrence due to the

1 delay in peak drug effect.

2 Now, let's look at the primary endpoint of  
3 drug liking Emax. The PD assessment of drug liking  
4 Emax used the zero to 100 bipolar visual analog  
5 scale where zero is a strong negative response, a  
6 score of 50 is a neutral response, and a score of  
7 100 is a strong positive response. Here we show  
8 the drug liking Emax for 40 milligrams of REMOXY,  
9 both manipulated and intact, was significantly  
10 lower than 40 milligrams of crushed oxycodone IR.

11 Drug high Emax was measured using a zero to  
12 100 unipolar scale where zero was no effect and 100  
13 was maximum at the moment high or euphoric effect.  
14 Drug high Emax for manipulated and intact REMOXY ER  
15 were significantly lower than crushed oxycodone IR.  
16 Manipulated REMOXY compared to IR oxycodone showed  
17 a 46.1 millimeter lower Emax, while intact REMOXY  
18 showed a 45.2 millimeter lower Emax.

19 This figure shows the mean drug liking  
20 scores following nasal administration over time.  
21 It supports the observation that REMOXY manipulated  
22 and intact were less liked than crushed

1 IR oxycodone for 8 hours following intranasal  
2 administration.

3 Take drug again is another important  
4 assessment in evaluating the abuse potential of  
5 drugs. This slide shows that at 12 hours, there  
6 was a significant difference in take drug again for  
7 both manipulated and intact REMOXY when compared to  
8 crushed oxycodone IR. The difference on a bipolar  
9 scale was 28.8 millimeters for manipulated REMOXY  
10 and 24.9 millimeters for intact REMOXY ER.

11 Consistent with the 12-hour take drug again  
12 results, there was a statistical difference between  
13 manipulated and intact REMOXY when compared to  
14 crushed oxycodone IR at the 24-hour time point. In  
15 addition, all the secondary endpoints were  
16 statistically significant in favor of manipulated  
17 and intact REMOXY compared to immediate-release  
18 oxycodone. The objective measurement of a  
19 difference in pupil constriction was consistent  
20 with subjective PD assessments.

21 In summary, intranasally administered  
22 manipulated and intact REMOXY ER showed

1 significantly less liking when compared to nasally  
2 administered immediate-release oxycodone. Subjects  
3 significantly preferred IR oxycodone over nasal  
4 REMOXY ER at all time points. Secondary endpoints  
5 were consistent with the primary endpoints, and PD  
6 was consistent with the PK results. Finally,  
7 REMOXY ER maintained extended-release profile when  
8 manipulated, suggesting less abuse potential than  
9 the comparator.

10 Dr. Friedmann will now present the clinical  
11 development of REMOXY ER.

12 **Applicant Presentation - Nadav Friedmann**

13 DR. FRIEDMANN: Good morning. My name is  
14 Nadav Friedmann. I'm the chief operating and  
15 medical officer for Pain Therapeutics. This  
16 morning, I will discuss product profile of REMOXY,  
17 the goals of the clinical program, and the safety  
18 and efficacy of the product.

19 As you have seen before, REMOXY is oxycodone  
20 based in a sealed capsule. If approved, it will be  
21 available in 5 milligram to 40 milligram strength.  
22 It will be administered twice daily for the

1        indication of management of pain severe enough to  
2        require daily, around-the-clock, long-term opioid  
3        treatment for which alternative treatment options  
4        are inadequate.

5                The goal of the clinical program was to  
6        demonstrate the safety and analgesic effect of  
7        REMOXY administered twice daily to patients with  
8        moderate to severe chronic pain. The efficacy  
9        program was developed in close collaboration with  
10       the FDA through a special protocol assessment. A  
11       special protocol assessment is a process in which  
12       there's a declaration from the FDA that the trial  
13       design, including patient selection, clinical  
14       endpoints, and statistical analysis are acceptable  
15       for FDA approval should the study be successful,  
16       and in this case, it was.

17               Study PTI-821-C0 compared the analgesic  
18       effect of REMOXY ER versus placebo in a chronic  
19       patient population. It was a 12-week,  
20       double-blind, randomized, placebo-controlled  
21       multicenter in 412 patients with moderate to severe  
22       chronic pain due to osteoarthritis of the hip or

1 knee.

2           On the next slide, you'll see the schematic  
3 of the study design. Following a washout period,  
4 patients were titrated in an open fashion for  
5 2 weeks from 5 milligrams to 20 milligrams of  
6 REMOXY ER. Following the titration, patients were  
7 then randomized in a double-blind fashion to either  
8 REMOXY ER or placebo. Placebo patients were  
9 titrated down over a 2-week period to preserve the  
10 blind.

11           REMOXY ER patients had the ability to either  
12 increase or decrease the dose for the first 4 weeks  
13 of the study, and then the last 8 weeks of the  
14 study, all doses were fixed. At the end of the  
15 study, again to preserve the blind, patients will  
16 tapered down.

17           REMOXY met the primary endpoints with a  
18 statistical significance of 0.007. The primary  
19 endpoint was the area under the curve of the pain  
20 intensity compared to placebo. REMOXY also met all  
21 secondary endpoints related to pain that were  
22 measured during that study such as quality of

1 analgesia, global assessment, and others. Adverse  
2 effects occurred in that study shown here that  
3 occurred at a frequency greater or equal to  
4 5 percent of the patient population. No new or  
5 unexpected adverse events were noted in this study.

6 I will now address the total package that we  
7 have on REMOXY in terms of patients involuntary  
8 exposure. This slide summarizes the total exposure  
9 of REMOXY ER/ Over 2400 patients were administered  
10 REMOXY of which 469 were administered for 6 months  
11 and 381 for 1 year. Overall, the side effects  
12 profile was similar to that of other opioid drug  
13 products, and there were no new or unexpected  
14 adverse events.

15 In summary, in a double-blind study, REMOXY  
16 met the primary efficacy endpoint, statistically  
17 significant at 0.00-7 and all secondary endpoints  
18 related to pain. The safety profile is consistent  
19 with that of other opioid drug products. I will  
20 now ask Dr. Steve Montgomery to present excipient  
21 risk management, which are related to unintended  
22 route of administration.

1                   **Applicant Presentation - Stephen Montgomery**

2                   DR. MONTGOMERY: Good morning. My name is  
3 Stephen Montgomery, and I am a toxicology  
4 consultant to PTI. I will be presenting  
5 information on systemic exposure on the only  
6 2 excipients and 2 decomposition products that were  
7 detected in an in vitro extraction study.

8                   The in vitro excipient extraction study was  
9 conducted at an independent laboratory. REMOXY  
10 40-milligram capsule samples were manipulated and  
11 extracted according to category 1 conditions.  
12 Analytical methods were developed and limits of  
13 quantitation established.

14                  Only 2 excipients Triacetin and hydroxyethyl  
15 cellulose, or HEC, and to excipient decomposition  
16 products, acetic acid and myristic acid, were  
17 detected. The highest level detected  
18 for Triacetin was 18.63 milligrams per milliliter,  
19 and for HEC, it was 1.52 milligrams per milliliter  
20 with manipulation R11 [sic] at extraction  
21 temperature E at time J. Levels of acetic acid and  
22 myristic acid were detected at or slightly above

1 the LOQ, each at a single time point.

2 Our evaluation involved searching the  
3 published scientific literature with a focus on  
4 intravenous studies with Triacetin, HEC, acetic  
5 acid, and myristic acid. Where possible, an  
6 attempt was made to identify a no adverse effect  
7 level and to calculate a margin of safety relative  
8 to the level of the extracted excipient or  
9 decomposition product from 2 REMOXY 40-milligram  
10 capsules.

11 Triacetin is a triester of glycerin and  
12 acetic acid, which are rapidly hydrolyzed in  
13 tissues to yield systemic exposures to glycerol and  
14 acetic acid. The high LD50 values with IV  
15 injection indicate that Triacetin has a very low  
16 potential for systemic toxicity.

17 In a repeated-dose study in animals  
18 receiving 31,600 milligrams per kilogram IV as a  
19 daily infusion showed no evidence of toxicity.  
20 This is concordant with the absence of toxicity  
21 associated with high oral doses of Triacetin in  
22 repeated-dose animal studies. The margin of safety

1 based on the 7-day repeated-dose IV study relative  
2 to the amount quantified in the in vivo extraction  
3 study was greater than 10,000-fold.

4           Excipient vapors that were evolved under  
5 certain conditions of REMOXY ER manipulated, noted  
6 by a previous speaker, were identified as  
7 Triacetin. Inhalation of exposure to saturating  
8 vapors of Triacetin for 6 hours per day for 5 days  
9 showed no evidence of respiratory, nasal, or ocular  
10 irritation, indicating a low potential for local  
11 effects from evolving REMOXY ER vapors. In studies  
12 to evaluate ocular irritation, only one was  
13 suggestive of a transient irritation with direct  
14 application of Triacetin, indicating a low or a  
15 minimal risk.

16           HEC is a celluloid polymer similar to other  
17 cellulose-based polymers that are currently  
18 approved in other opioid ER formulations. It is  
19 listed in the FDA inactive ingredient database, the  
20 IID, for use in approved oral, ophthalmological,  
21 otic, and topical drug products. It is inert at  
22 high acute and repeated oral dose in animals.

1           HEC is not readily metabolized, and  
2 therefore systemic clearance slowly occurs via the  
3 reticuloendothelial system. Information on acute  
4 systemic exposure to HEC is quite limited and  
5 varied depending on the species and delivery  
6 methods. Low acute toxicity values with systemic  
7 exposures in some rodent studies has not been  
8 affirmed in non-rodent studies have longer  
9 duration.

10           Toxicity was not reported following a single  
11 intravenous injection of 1200 milligrams per  
12 kilogram. Repeated IV injections of HEC have been  
13 associated with hemodilution, hepatic, and renal  
14 storage, and vascular lesions in some studies. The  
15 margin of safety based on the acute IV study  
16 relative to the amount quantified in the in vitro  
17 extraction study was greater than 4800-fold.

18           Acetic acid is a natural constituent readily  
19 metabolized in most tissues. This is absorbed  
20 orally from intake of foods, providing for the  
21 endogenous levels of acetic acid. The level of  
22 acetic acid detected in the in vitro extraction

1 study was below 0.4 percent, the amount listed in  
2 the FDA inactive ingredient database for use in  
3 approved IV drug products, and therefore does not  
4 present a safety concern at the level detected.

5 Acute toxicity IV50 values would suggest  
6 that acetic acid may have low to moderate potential  
7 for adverse effects if given by this route of  
8 administration. However, considering a safety  
9 margin of 21,000-fold for the low level of acetic  
10 acid detected in the in vivo extraction study  
11 seemed very unlikely.

12 Myristic acid is a natural C14 fatty acid  
13 metabolized in the intestine and systemically via  
14 the beta oxidation pathway. Myristic acid is  
15 absorbed orally following food intake; hence,  
16 providing for the endogenous human plasma  
17 concentrations. The IV50 value of 43 milligrams  
18 per kilogram would suggest that myristic acid may  
19 have a potential for acute toxicity. However, oral  
20 studies in animals have shown myristic acid to be  
21 relatively non-toxic.

22 Based on the IV LD50 value, the safety

1 margin was calculated as 4300 fold based on the  
2 amount extracted from 2 REMOXY ER capsules. Given  
3 the endogenous plasma concentrations, it would seem  
4 unlikely that systemic exposure to myristic acid at  
5 the level detected in the in vitro extraction study  
6 would pose a safety concern.

7 In summary, the margin of safety for  
8 systemic exposure to Triacetin at the maximum  
9 amount extracted is greater than 10,000-fold and  
10 for HEC is 4800-fold relative to the levels  
11 detected in the in vitro extraction of manipulated  
12 REMOXY ER 40-milligram capsules. In conclusion,  
13 the results show a low risk for Triacetin, HEC,  
14 acetic acid, and myristic acid for acute adverse  
15 systemic effects with misuse.

16 I will now ask Dr. Michael Marsman to  
17 discuss the risk mitigation strategy for REMOXY ER.

18 **Applicant Presentation - Michael Marsman**

19 DR. MARSMAN: Thank you, Dr. Montgomery.

20 Good morning, everyone. As the slide  
21 states. my name is Mike Marsman, and I'm  
22 responsible for regulatory affairs at Pain

1 Therapeutics. This morning, I'd like to give you  
2 just a brief overview of our risk mitigation  
3 strategy as well as summarizing the risk-benefit  
4 profile for REMOXY ER.

5 As sponsor of an extended-release opioid  
6 product, we are very serious about our  
7 responsibilities to assure safe use of REMOXY once  
8 it's on the market. Accordingly, we plan to assure  
9 that strong risk mitigation strategies are in place  
10 following approval. This will include full  
11 participation in the class-wide REMS activities, a  
12 comprehensive drug safety and pharmacovigilance  
13 program, and procedures to assure safe packaging,  
14 distribution, and disposal of our product.

15 As indicated on the slide, Pain Therapeutics  
16 currently has observer status in the industry-wide  
17 REMS consortium, and we plan to convert to full  
18 active membership upon approval, and that will  
19 include full participation in the REMS educational  
20 activities and post-approval study activities.

21 To summarize the risk-benefit profile,  
22 REMOXY demonstrates a favorable risk-benefit

1 profile. It met the clinical endpoints in a large,  
2 well-controlled, phase 3 efficacy study. The  
3 safety profile is similar and consistent with other  
4 ER opioid products. There were no new or  
5 unexpected adverse events identified. And based on  
6 the totality of the category 1, 2, and 3 study  
7 results, REMOXY can be expected to meaningfully  
8 deter injection, nasal, and smoking routes of  
9 abuse.

10 In conclusion, abuse resistant or abuse  
11 deterrent formulations such as REMOXY can play an  
12 important role against prescribed opioid abuse  
13 while still ensuring appropriate access to patients  
14 suffering from chronic pain. REMOXY's unique  
15 formulation is an advancement to the science of  
16 abuse deterrence. It increases the range of  
17 available abuse-deterrent technologies. It  
18 provides another treatment option for chronic pain.  
19 It addresses the vulnerabilities that exist with  
20 some currently marketed ER oxycodone products. And  
21 it demonstrates properties that can be expected to  
22 deter abuse by the nasal snorting, injection, and

1 smoking routes of administration.

2 Finally, I'd like to express our  
3 appreciation to the committee for their attention  
4 to our presentation this morning and to thank FDA  
5 for working with us throughout the development  
6 process. Thanks to both of you. And I'll now turn  
7 the podium over to Dr. Friedmann for any clarifying  
8 questions. Thank you again.

9 **Clarifying Questions**

10 DR. McCANN: Are there any clarifying  
11 questions for Pain Therapeutics? Please remember  
12 to state your name for the record before you speak.  
13 If you can, please direct your questions to a  
14 specific presenter. Ms. Spotila?

15 MS. SPOTILA: Jennifer Spotila. My  
16 question's for Dr. Crowley. In your presentation,  
17 you said that design of the in vitro work was  
18 informed, in part, by recreational opioid abusers,  
19 and you mentioned internet forums. Was that your  
20 only source of information from those abusers?

21 DR. CROWLEY: Yes. We read several internet  
22 sites to see what the abuse community was doing to

1       manipulate and abuse existing commercial products.

2               DR. McCANN:   Dr. Meisel?

3               DR. MEISEL:   Steve Meisel, Fairview.  A  
4       question for Dr. Montgomery about the toxicity.  I  
5       appreciate the information you gave, but it seemed  
6       like it was focused on what happens if you would  
7       try to extract these chemicals.  I want to focus on  
8       what happens when you use this drug as intended.  
9       So what is the absorption of these ingredients,  
10      plus the ingredients that you didn't mention that  
11      are in there as the excipients?

12              What happens when used correctly?  How much  
13      of it is absorbed?  What are the anticipated  
14      adverse effects of these ingredients, not when  
15      extracted and injected, but when ingested in the  
16      designed way?

17              DR. FRIEDMANN:  We have done full toxicology  
18      on those products, and we'll try to show you what  
19      we did.

20              DR. MONTGOMERY:  Yes, we've done a full  
21      complement of toxicology studies normally required  
22      for these individual components.  Let's see if we

1 can get the slide up here. Basically, in running  
2 these studies with an oral administration, they're  
3 relatively non-toxic. In other words, we don't see  
4 much happening with huge oral doses, 2,000 to 4,000  
5 milligrams per kilogram per day.

6 So you can see the listing over here of the  
7 number of studies -- of the types of studies, which  
8 were completed, including acute subchronic; chronic  
9 toxicity studies, which are 6 months or longer;  
10 genotoxicity studies usually in in vitro and in  
11 vivo; carcinogenicity studies; reproduction  
12 studies, which includes seg 1 [ph], seg 2, seg 3;  
13 fertility reproduction, teratology, and  
14 perinatal/postnatal studies in some cases; and  
15 other toxicity studies.

16 DR. MEISEL: Well, I'm not sure that really  
17 answers any detailed questions. Specifically, I  
18 just did a quick Wikipedia search on myristic acid,  
19 and it talks about the fact that it has the  
20 potential of raising somebody's cholesterol and  
21 triglyceride. And if that happens, what are the  
22 long-term impacts if you take something that raises

1 somebody's cholesterol and triglyceride on their  
2 cardiovascular risk factors?

3 DR. MONTGOMERY: Well, in these particular  
4 studies -- for example, for the chronic oral  
5 toxicity studies -- we would do a complete battery  
6 of CMC work, which would include everything from  
7 hematology, clinical chemistry, and urinalysis  
8 using rats and dogs. And when we do those, we take  
9 a look and see whether or not there are any changes  
10 in lipid values, for example, or any changes in  
11 hematology parameters, et cetera.

12 As said, the studies which were done, there  
13 was almost no toxicity that was associated with any  
14 of them, particularly the Triacetin.

15 DR. CROWLEY: With respect to your last  
16 question, myristic acid is not an inactive  
17 ingredient. It was a degradant formed following a  
18 manipulation, and small amounts were observed  
19 during an extraction.

20 DR. McCANN: Dr. Nelson?

21 DR. NELSON: Thanks. I have two questions  
22 for Dr. Friedmann. Lewis Nelson. I'll just put

1       them together, and you can answer them in any order  
2       you like, if you don't mind.

3               My first question is, as I read the efficacy  
4       study that you designed, it looks like it's an  
5       enrolled enrichment and controlled withdrawal  
6       study. And I wonder why you didn't do a study that  
7       was randomized at inception in an unscreened  
8       population, which would probably be more true to  
9       form of how things worked in the real world.

10              My other question is, what is the  
11       implication of the proposed indication, the last  
12       line of which says, "for which alternative  
13       treatments are inadequate," what are the  
14       alternative treatments that you're suggesting are  
15       inadequate? Are these other opioids or is this  
16       meant to be a first-line opioid that people go to  
17       when they have chronic pain?

18              DR. FRIEDMANN: Answering your first  
19       question, why did we do the enriched design, I have  
20       done a phase 2 study earlier, where we actually  
21       started the 10 milligram as a first dose, the  
22       10 milligram twice a day, and the dropout was quite

1 high. And that's why we elected to develop the  
2 5 milligram as a titration dose to move up. And  
3 the second study when we did the large efficacy  
4 study, the dropout was a little less and patients  
5 tolerated it better.

6 Does that answer the first question?

7 DR. NELSON: It answers the enrollment, the  
8 enriched enrollment part. But what about the  
9 controlled withdrawal? Why didn't we just start  
10 everybody from inception on medications rather than  
11 get everybody hyperalgesic or tolerant, and then  
12 stop them.

13 DR. FRIEDMANN: Because the dropout is going  
14 to be fairly high if you want to titrate them up  
15 to -- if you start at 10 and you go up higher, the  
16 dropout was just too high in that study.

17 Secondly, as I mentioned earlier, this study  
18 was designed, together with the FDA, as a special  
19 protocol assessment, and everything was agreed to.  
20 And the alternative therapy, that's classic for all  
21 the opioids basically, given to us by the FDA. And  
22 alternative therapies would be the non-steroidal,

1 anti-inflammatories, for example.

2 DR. McCANN: Dr. Zibbell?

3 DR. ZIBBELL: Jon Zibbell, RTI  
4 International. I know the injection abuse studies,  
5 you said that there was no syringeability and  
6 injectability. A lot of times in the real world,  
7 we don't know what other things people are going to  
8 use to be able to manipulate those. Let's say they  
9 could manipulate those and inject that formulation.  
10 Would there be any vein damage or could you see any  
11 damage physiologically if those drugs were  
12 injected? Is there any evidence for those  
13 excipients causing harm if injected?

14 DR. FRIEDMANN: That's a two-point answer.  
15 Number one, we have done studies where you take  
16 from oxy at special temperatures that would  
17 force [indiscernible] injection, and put it in  
18 blood, and there's no extraction. So there's no  
19 reason for somebody -- it will not be a good reason  
20 for somebody to even inject it because they're not  
21 going to get any high. That's number one.

22 Number two, in terms of the second portion

1 of your question, the extraction studies, what we  
2 try to show is how much oxycodone you will get  
3 during the extraction for an IV injection; and as  
4 you saw, very little you're going to get from the  
5 extraction.

6 Does that answer your question?

7 DR. ZIBBELL: Sure. Thanks.

8 DR. McCANN: Dr. Ciccarone?

9 DR. CICCARONE: Dan Ciccarone, UCSF. This  
10 if for Dr. Webster. Concerning the human abuse  
11 potential studies, it seems that on a few of the  
12 comparators, there was both OxyContin IR  
13 manipulated -- I'm sorry, oxycodone IR manipulated  
14 and OxyContin branded ER manipulated, but not for  
15 all. I'm wondering why OxyContin ER was not used  
16 in all of those studies.

17 DR. FRIEDMANN: Let me answer that question.  
18 We designed the study and discussed it with the  
19 FDA. The thought was just run a study against a  
20 OxyContin. Why do a study against an IR? That's  
21 going to be our comparator. The impression that I  
22 received from the FDA was that it's probably better

1 to run it against the IR because there's more  
2 information available, and that's a standard that  
3 we should run against.

4 So the study was going to go against the IR  
5 and no OxyContin. And then as a second thought, I  
6 said, well, why don't we see how is OxyContin doing  
7 in an open stud. So the study itself was a 4-way  
8 crossover study without OxyContin, and then we took  
9 the first 20 volunteers, and we gave them OxyContin  
10 manipulated just to see the PK on that.

11 DR. McCANN: Dr. Arfken, please?

12 DR. ARFKEN: Cynthia Arfken, Wayne State  
13 University. I have two questions. What is the age  
14 range for which you are seeking permission? And  
15 the next one is, what are the demographics of the  
16 people who participated? I'm especially interested  
17 in the age range as well as that they're both women  
18 and men involved in these studies.

19 DR. FRIEDMANN: Which study are we talking  
20 about?

21 DR. ARFKEN: I'm interested in all the  
22 studies.

1 DR. FRIEDMANN: I missed -- well, both men  
2 and women were in all the studies. That's to  
3 answer the second question. The first question, I  
4 didn't quite understand.

5 DR. ARFKEN: The age range that you're  
6 seeking approval for.

7 DR. FRIEDMANN: Well, in the osteoarthritis  
8 study, obviously, the age range was for the older  
9 population, although we have a fair amount between  
10 the age of 30 and 40. In the abuse-deterrent  
11 population, the HIP [ph] studies, the population  
12 was younger, most men and women.

13 DR. ARFKEN: So are you asking for approval  
14 for the adult population only?

15 DR. FRIEDMANN: We're asking for approval  
16 from 18 years and older, yes.

17 DR. McCANN: Ms. Robotti?

18 MS. ROBOTTI: Hi. This is Sue Robotti.  
19 During Dr. Meisel's question, slide number 34 was  
20 put up on the screen. I think Dr. Friedmann was  
21 talking, although I don't remember. There was a  
22 note made that you did studies on reproductive

1 toxicity. Could you talk about those studies?

2 DR. FRIEDMANN: Thirty-four?

3 DR. ROBOTTI: It's not from the original  
4 presentation; it was from when Dr. Meisel asked a  
5 question. That's not the slide.

6 DR. MONTGOMERY: Well unfortunately, I  
7 didn't do the study, so I can't really speak to  
8 them very much. IT's the one before this. And my  
9 colleague who did do them is, unfortunately,  
10 recovering in the hospital for back surgery, so I  
11 would be happy to talk with you a little bit later  
12 perhaps about exactly what was done.

13 DR. ROBOTTI: Will it affect the guidelines  
14 or the labeling? Will you have information for  
15 pregnant women or lactating women? Am I  
16 misunderstanding what reproductive toxicity is?  
17 What is reproductive toxicity?

18 DR. MONTGOMERY: I'm sorry?

19 DR. ROBOTTI: What is reproductive toxicity?

20 DR. MONTGOMERY: These are studies that are  
21 done --

22 DR. KLUETZ: Microphone, please.

1 DR. MONTGOMERY: Reproductive toxicity  
2 studies are done to assess the effects of the drugs  
3 or the inactive ingredients on fertility and  
4 reproductive, on teratology, and on -- in some  
5 cases, we'll also look at perinatal/postnatal  
6 development.

7 DR. ROBOTTI: So I'm just asking if that  
8 will come into play during the labeling.

9 DR. MONTGOMERY: Yes.

10 DR. ROBOTTI: I'm not sure if that's a --

11 DR. MONTGOMERY: It would come into play.

12 DR. ROBOTTI: So information on that would  
13 be helpful. Thanks.

14 DR. HERTZ: This is Sharon Hertz. I think  
15 the question is, are we going to be able to discuss  
16 this part of the labeling today, and we don't  
17 typically. So I think the next question -- I don't  
18 want to tell you what questions to ask the sponsor,  
19 but we're not planning to present toxicology data.  
20 So if you have questions about the results of the  
21 studies and how it may affect labeling, we're not  
22 going to have that information either.

1 DR. ROBOTTI: Okay, because use of opioids  
2 during pregnancy and lactation, there's often not a  
3 huge amount of information. So if there were  
4 studies done on this and that information's going  
5 to be on the label, that would be -- that should be  
6 discussed. The information should be available to  
7 the panel.

8 DR. HERTZ: Right. So you might want to  
9 query the sponsor more.

10 DR. ROBOTTI: So that's my question. Are  
11 you requesting -- are you going to be asking to put  
12 information on pregnancy and lactation use on the  
13 label? And if so, will you give us that  
14 information?

15 DR. FRIEDMANN: We're not asking for it.

16 DR. McCANN: With that --

17 DR. HERTZ: This is Sharon Hertz again.  
18 Sorry. There are several sections that are  
19 required as part of labeling, and information about  
20 sex from reproductive toxicology studies are a part  
21 of that. If you want more information on that,  
22 perhaps the section of labeling that's relevant

1 might be displayed. I just feel like there's a  
2 disconnect between the questions and the discussion  
3 right now, so I'm just putting that out there, if  
4 the sponsor would care to display the proposed  
5 label, the relevant sections to the repro-tox.

6 DR. FRIEDMANN: I'd just like to mention  
7 that all the studies we have done on the excipients  
8 of toxicology was done according to guidance for  
9 the excipients and for REMOXY. We also have done a  
10 study with the complete formulation in guinea pigs.

11 DR. McCANN: So we have about 5 or 6 more  
12 questions to go, but what I'd like to do at this  
13 point is take a very short break and come back by  
14 about 11:18. Then we'll start with the FDA and get  
15 to the questions after the FDA's presentations.  
16 Thank you.

17 (Whereupon, at 11:07 a.m., a recess was  
18 taken.)

19 DR. McCANN: We will proceed with the FDA  
20 presentations.

21 **FDA Presentation - James Tolliver**

22 DR. TOLLIVER: Good morning. My name is

1 James Tolliver. I'm a pharmacologist for the  
2 controlled substance staff within the Office of the  
3 Center Director, Center for Drug Evaluation and  
4 Research at the FDA. This morning, I would like to  
5 briefly discuss oral human abuse potential study  
6 B4501016, submitted under NDA 22324 for REMOXY ER  
7 capsules. I also intend to make a few comments  
8 regarding the category 1 smoking study conducted  
9 with REMOXY ER.

10 The oral study is a randomized,  
11 double-blind, triple-dummy placebo and active  
12 controlled single-dose, 4-way crossover design  
13 utilizing an evaluable population of  
14 46 non-dependent recreational opioid users.  
15 Treatments included placebo; REMOXY ER capsules, 40  
16 milligrams intact swallowed; REMOXY ER capsules, 40  
17 milligrams chewed for 5 minutes; and oxycodone  
18 hydrochloride IR 40-milligram tablets crushed and  
19 placed in solution as the positive control.

20 Statistical analyses of pharmacodynamic  
21 measures were conducted by the CDER, Office of  
22 Biostatistics, using where possible a mixed-effects

1 model. The primary comparison was that of REMOXY  
2 40 milligrams chewed versus oxycodone hydrochloride  
3 IR, 40 milligrams crushed.

4 The pharmacodynamic measures of interest  
5 will include the zero to 100-millimeter unipolar  
6 visual analog scales, or VAS, for drug liking high,  
7 take drug again, and overall drug liking. The  
8 3 unipolar scales of drug liking, high, and overall  
9 drug liking were anchored on the left by zero, not  
10 at all, and on the right by 100 extremely. In the  
11 case of take drug again VAS, the anchor on the left  
12 was zero, definitely not, and on the right by 100,  
13 definitely so.

14 Drug liking VAS and high VAS are at the  
15 moment subjective measures taken at selective time  
16 intervals following start of treatment. In the  
17 case of drug liking, subjects are asked to respond  
18 to the statement, "At the moment, my drug liking  
19 for this drug is." For the high VAS, subjects are  
20 asked to respond to the statement, "I am feeling  
21 high."

22 Take drug again VAS and overall drug liking

1 VAS are taken at 24 hours after dosing when the  
2 drug effect has largely subsided. Subjects were  
3 asked to reflect back over each treatment. In the  
4 case of take drug again VAS, subjects are asked to  
5 respond to the statement, "I would take this drug  
6 again." For overall drug liking, subjects are  
7 asked to respond to the statement, "Overall, my  
8 liking for this drug is."

9           There were four primary endpoints in the  
10 study, including maximum effect designated Emax for  
11 unipolar drug liking and high, and in addition,  
12 cumulative experience of drug liking and high out  
13 to 2 hours post-dosing, designated area under the  
14 effect curve or  
15 AUE zero to 2 hours.

16           The results for the primary endpoints are  
17 provided in the table on this slide for all four  
18 treatments. Treatments constituting the primary  
19 comparison, namely REMOXY chewed versus oxycodone  
20 hydrochloride IR crushed in solution, are provided  
21 in the yellow columns. What I would like for you  
22 to notice about this slide is that for both of

1 these treatments, the resulting mean values for  
2 Emax and area under the effect curves out to  
3 2 hours for both drug liking and high were higher  
4 than that produced by either placebo or REMOXY  
5 swallowed intact.

6 This slide provides the statistical analyses  
7 for the primary comparison. The Emax and drug  
8 liking for REMOXY chewed was not smaller than that  
9 produced by the comparator oxycodone  
10 hydrochloride IR crushed. In addition, the Emax of  
11 high was statistically smaller for REMOXY chew  
12 compared to oxycodone hydrochloride IR. However,  
13 there was a failure to demonstrate a minimum of  
14 5 percent reduction in mean Emax of high for REMOXY  
15 chewed compared to oxycodone hydrochloride IR  
16 crushed. REMOXY chewed resulted in limited but  
17 statistically significant reductions at area under  
18 the effect curve out to 2 hours compared to  
19 oxycodone hydrochloride IR crushed for both drug  
20 liking and high VAS.

21 The slide provides the secondary endpoints  
22 for the Emax of take drug again and overall drug

1 liking VAS. Again, the treatments constituting the  
2 primary comparison, namely REMOXY chewed versus  
3 oxycodone hydrocodone chloride IR crushed, are  
4 provided in yellow. Note that following these two  
5 treatments, least squared mean Emax, for both  
6 measures were in the range of 60 to 65 millimeters,  
7 which are well above the means values produced by  
8 either placebo or REMOXY swallowed intact.

9           Statistical analyses for the primary  
10 comparisons for Emax unipolar take drug again and  
11 unipolar and overall drug liking are provided in  
12 this slide. Numerically, the mean differences of  
13 Emax for take drug again and overall drug liking,  
14 produced by REMOXY chewed, was lower by 1.5 and  
15 3.8 millimeters, respectively, compared to that  
16 produced by oxycodone hydrochloride IR crushed.  
17 These small differences were not statistically  
18 significantly different. As such remarks, REMOXY  
19 chewed when compared to oxycodone hydrochloride IR  
20 crushed was not associated with a lower Emax for  
21 either take drug again or for overall drug liking.

22           This slide provides some conclusions

1 regarding the oral study. There were three  
2 findings of this study when considering the primary  
3 comparison. First, REMOXY chewed compared to  
4 oxycodone hydrochloride IR crushed was not  
5 associated with significant reductions in Emax for  
6 the unipolar visual analog scales for drug liking,  
7 take drug again, or overall drug liking.

8           Secondly, although statistically  
9 significant, the reduction in Emax of unipolar high  
10 VAS produced by REMOXY chewed versus oxycodone  
11 hydrochloride IR crushed was limited, raising the  
12 question of clinical relevance.

13           Third, early drug liking and high experience  
14 reflected in the area under the effect curve out to  
15 2 hours post-dosing was lower but limited for  
16 REMOXY chewed compared to oxycodone hydrochloride  
17 IR crushed.

18           When considering these findings together, we  
19 conclude that there are no data to support that  
20 limited differences in the early drug liking or  
21 high experience over the first 2 hours are  
22 clinically relevant findings consistent with

1 possible abuse-deterrent effects, especially  
2 considering that the Emax analyses for drug liking,  
3 high, take drug again, an overall drug liking in  
4 this study failed to demonstrate abuse-deterrent  
5 effects of REMOXY.

6 I'd like to turn for a moment to the  
7 category 1 smoking study, which was conducted under  
8 protocol coded V1. Under this protocol, the  
9 percentages of labeled dose of oxycodone from  
10 manipulated REMOXY 40 milligrams and 40 milligrams  
11 of the active comparator recovered from vapor were  
12 3.8 and 10.7, respectively. Overall, this  
13 percentage difference reflecting 2.76 milligrams of  
14 oxycodone was limited.

15 The 4.28 milligrams of oxycodone quantitated  
16 in the total collected vapor from the active  
17 comparator might be expected to produce subjective  
18 effects in non-dependent recreational opioid drug  
19 abusers if all the vapor was inhaled. However, the  
20 methods used to collect and assay, the oxycodone  
21 and vapor was artificial and does not reflect the  
22 real-world experience. Considering that

1 individuals would most likely capture only a  
2 limited percentage of the vapor, it is not clear  
3 whether subjective effects would be obtained using  
4 the positive active comparator.

5 Finally, my last slide, I would like to  
6 comment on the assertion that Triacetin, an  
7 excipient found in the REMOXY formulation, might  
8 serve as a deterrent to smoking the REMOXY  
9 formulation. This substance may be volatilized,  
10 and the resulting vapor may serve as an irritant to  
11 the respiratory track and eyes. However, any  
12 consideration of Triacetin serving an  
13 abuse-deterrent effect to smoking of REMOXY would  
14 require confirmation of significant irritant  
15 effects as documented in human subjects smoking  
16 REMOXY.

17 At the same time, based upon ethical  
18 considerations, the administration of REMOXY to  
19 human subjects by smoking for purposes of  
20 evaluating irritant or subjective effects cannot be  
21 done. Considering the limited amount of oxycodone  
22 recovered in the vapor it is not clear that the use

1 of Triacetin as a potential aversive agent would be  
2 warranted. Thank you.

3 **FDA Presentation - Mallika Mundkur**

4 DR. MUNDKUR: My name is Mallika Mundkur.  
5 I'm a medical officer within the office of  
6 Surveillance and Epidemiology, and I'll be  
7 reviewing the recent epidemiologic data on use,  
8 misuse, and abuse of oxycodone. Aligned with  
9 recommendations from a 2017 report released by the  
10 National Academies of Sciences, Engineering, and  
11 Medicine, FDA continues to consider public health  
12 throughout the life cycle of opioid products.  
13 Public health considerations include both  
14 unintended consequences as well as use in  
15 non-target populations.

16 In that context, the purpose of this review  
17 is to provide the committee with a relevant public  
18 health framework to consider alongside other data.  
19 Our two objectives are as follows: first to review  
20 high-level data regarding the utilization of  
21 oxycodone products; and second, to review  
22 epidemiologic data on misuse and abuse of

1       oxycodone-containing products and comparator drugs.

2               Of Note, many of the data sources we  
3       reviewed do not distinguish between  
4       extended-release versus immediate-release products.  
5       Thus, we describe data more generally and provide  
6       product-specific information when available.  
7       Additionally, to date, no postmarket data have been  
8       submitted to the FDA that support a meaningful  
9       effect of ADFs on reductions in abuse, misuse, or  
10      related adverse clinical outcomes in the community.  
11      Therefore, published studies attempting to evaluate  
12      these outcomes will not be presented.

13              We will begin by presenting data on  
14      utilization extracted from IQVIA national  
15      prescription audit. The specific questions we  
16      sought to answer were the following: How  
17      frequently are specific oxycodone products  
18      dispensed in the U.S.? Among extended-release and  
19      long-acting products, which are the most frequently  
20      dispensed products? Among products intended to  
21      deter abuse, which are the most frequently  
22      dispensed? And finally, what are the trends in

1 dispensing for any of the above?

2           This figure shows the nationally estimated  
3 number of dispensed prescriptions for  
4 oxycodone-containing products from U.S. outpatient  
5 retail pharmacies over the period of 2013 to 2017.  
6 Overall levels of dispensed oxycodone prescriptions  
7 peaked in 2015 at \$56 million and have decreased to  
8 \$50 million by 2017. The vast majority of  
9 oxycodone prescriptions in 2017 were either  
10 combination or single-entity oxycodone  
11 immediate-release products, while fewer than  
12 8 percent were for an oxycodone extended-release  
13 product.

14           In contrast with the previous slide, this  
15 figure includes not only oxycodone but other  
16 products as well for comparison. Among  
17 extended-release and long-acting opioid analgesics,  
18 morphine ER accounted for the largest proportion in  
19 2017 at approximately 33 percent, followed by  
20 fentanyl at 22 percent, and oxycodone ER at 20  
21 percent of all dispensed ER/LA prescriptions.

22           Here we see yearly estimates of

1 prescriptions dispensed for opioid analgesic  
2 products specifically formulated with properties  
3 intended to deter abuse. Reformulated OxyContin  
4 ER, delineated here by the green line, accounted  
5 for 88 percent of ADF products dispensed in 2017.  
6 The other oxycodone ER product currently available  
7 on the market, Xtampza ER, is delineated by the  
8 purple line at the bottom. There has been a  
9 downward trend in prescribing for reformulated  
10 OxyContin with 4.9 million prescriptions in 2013  
11 and 3.4 million in 2017.

12 In summary, in 2017, approximately 50  
13 million prescriptions for oxycodone were dispensed  
14 at outpatient retail pharmacies in the U.s. Among  
15 ER/LA opioids, oxycodone ER constituted 20 percent  
16 of all dispensed prescriptions, and among ADF  
17 products specifically, 88 percent of dispensed  
18 prescriptions were for reformulated OxyContin ER.

19 The second component of this review will  
20 focus on misuse and abuse of oxycodone-containing  
21 products and comparator drugs. With the second  
22 objective, we will address a number of questions,

1 including the following: What is the current scale  
2 of misuse and abuse of prescription opioids? Which  
3 are the most frequently abused opioids? What are  
4 the most common routes of abuse for opioids,  
5 including available abuse-deterrent formulations?  
6 And finally, what is the magnitude of morbidity and  
7 mortality associated with oxycodone-containing  
8 products versus comparator drugs?

9 The definitions of misuse and abuse used for  
10 the majority of this review are consistent with  
11 what FDA has previously issued in guidance to  
12 industry. Misuse is defined by FDA as the  
13 intentional therapeutic use of a drug product in an  
14 inappropriate way and specifically excludes the  
15 definition of abuse. Abuse is defined as the  
16 intentional non-therapeutic use of a drug product  
17 or a substance, even once, to achieve a desirable  
18 psychological or physiological effect.

19 We used a number of data sources that are  
20 described in detail in the background information  
21 provided. As we go through the results, we will  
22 provide a brief description of the relevant data

1 source.

2           Scale of misuse and abuse. According to the  
3 National Survey on Drug Use and Health, NSDUH, a  
4 federally funded household survey of individuals 12  
5 and older in the United States, the most frequently  
6 misused opioid products in the general population  
7 were hydrocodone and oxycodone, with misuse defined  
8 by NSDUH to include use of a drug in any manner  
9 other than as medically directed, including but not  
10 limited to abuse.

11           In this figure, we have the Y-axis on the  
12 left indicating the number of individuals in  
13 thousands who reported past year misuse of the  
14 drug, and the Y-axis on the right represents this  
15 number as a percentage of the total population.  
16 You can see there is no significant change in  
17 levels of oxycodone misuse from 2015 to 2016, and  
18 the total number of individuals reporting misuse of  
19 oxycodone in 2016 was 3.9 million or approximately  
20 1.5 percent of the total population.

21           In this figure, we have data from the  
22 National Poison Data System, a national network of

1     poison centers receiving calls from the public or  
2     healthcare workers. One strength of this data  
3     source is that it collects more detailed  
4     information on product formulation, and may be more  
5     accurate in that regard than other data sources.

6             This figure demonstrates that over 3,000  
7     calls per year reported intentional exposure to an  
8     oxycodone-containing product over the period 2012  
9     to 2016, with calls reporting exposure to IR  
10    products being much more frequent than those for ER  
11    products. A total of 50,000 calls reporting  
12    intentional exposure to an oxycodone product were  
13    placed over the entire time period, while by  
14    comparison, 75,000 calls were placed for  
15    hydrocodone, 9500 calls for morphine, and 24,000  
16    calls for heroin. In NPDS, intentional exposures  
17    include misuse, abuse, self harm, and other  
18    unclassified reasons for exposure.

19            Relative frequency of abuse; specific  
20    products. According to the Radars Treatment Center  
21    program, a surveillance program that includes  
22    surveys of individuals entering treatment for

1       opioid use disorder, 35 percent of individuals  
2       reported past month abuse of oxycodone.

3               This chart shows the percentage of  
4       respondents in the RADARS Treatment Center program  
5       who reported past month abuse of various opioid  
6       products with products grouped together on the  
7       X-axis by active pharmaceutical ingredient. In  
8       this population, oxycodone was the most frequently  
9       abused prescription product, though heroin was the  
10       most frequently abused overall.

11              Formulation-specific data from RADARS  
12       suggest more frequent abuse IR than ER products,  
13       though as noted here, 15 percent report past month  
14       abuse of an oxycodone ER product specifically.

15              When accounting for prescription volume, the  
16       relative frequency of oxycodone abuse compared with  
17       other products appears to change. This chart shows  
18       the rate of past month abuse per 100,000 dispensed  
19       dosage units by active pharmaceutical ingredient.  
20       Here we see that some of the more potent agents  
21       such as fentanyl and oxymorphone are abused more  
22       than other agents relative to what will be expected

1 from their overall levels of availability.  
2 Formulation-specific data in this case suggests  
3 that when adjusting for utilization, oxycodone ER  
4 appears to be abused more frequently than oxycodone  
5 IR.

6 Routes of abuse. We reviewed a number of  
7 articles that discussed routes of abuse for  
8 prescription opioids with the key results  
9 summarized in this table. From left to right, the  
10 columns for this table are the study author, data  
11 source used, the category of opioids assessed, and  
12 specific routes of abuse assessed in the study.

13 Two of these studies reported data on abuse  
14 of ADF products specifically. The Cassidy study,  
15 based upon data from the surveillance system  
16 NAVIPPRO, a system like RADARS, which surveys  
17 individuals entering treatment facilities for  
18 substance-use disorder, 60 percent of individuals  
19 reported oral abusive ADFs, 20 to 30 percent  
20 reported snorting, and 30 percent reported  
21 injection.

22 The Severtson analysis, a quarterly report

1 released by the RADARS Treatment Center program,  
2 reported similar numbers, though additionally  
3 providing data on chewing and smoking of ADFs  
4 products, endorsed among 25 percent and 5 percent  
5 of individuals, respectively. A study by Butler  
6 and colleagues, also using data from NAVIPPRO,  
7 though focused primarily on oxycodone ER, reported  
8 higher rates of oral abuse, similar rates of  
9 snorting, lower rates of injection, and similar  
10 rates of smoking as the prior studies.

11 Finally, a study by the Vietri and  
12 colleagues, identified by the sponsor, used a small  
13 sample of patients from the Kantar Health U.S.  
14 National Wellness survey and assessed abuse of all  
15 prescription opioids. This study reported very  
16 different numbers, potentially explained by the  
17 more heterogeneous category of opioids assessed,  
18 the smaller sample size relative to the other  
19 studies, or that the population in the Vietri study  
20 may represent patients with less advanced opioid  
21 use disorder. Another key difference is that the  
22 Vietri study assesses abuse in the past 3 months,

1 while the other studies assess abuse in the past  
2 month only.

3 The findings from these studies can be  
4 summarized as follows. For a sample of patients  
5 entering treatment for opioid or substance-use  
6 disorder, oral abuse was the most common, followed  
7 by snorting and injection, with smoking as a very  
8 infrequently reported route of abuse. For a sample  
9 of patients from the general population, data on  
10 routes of abuse for specific products such as  
11 oxycodone or not available, though for prescription  
12 opioids as a whole, oral abuse is much more common  
13 with snorting, injection, and smoking also reported  
14 as frequently attempted routes.

15 Finally, morbidity and mortality. According  
16 to the National Electronic Injury Surveillance  
17 System, NEISS-CADES, a database of a nationally  
18 representative sample of emergency department  
19 visits in the U.S., during 2016, there were nearly  
20 300,000 estimated ED visits for harms from  
21 prescription opioid products of which approximately  
22 40 percent involved oxycodone-containing products,

1 specifically.

2           This table summarizes ED visits moving from  
3 left to right, with the left column indicating  
4 opioid ingredient, then the number of cases in the  
5 sample, the weighted number of visits projected at  
6 the national level, and the percent of the total  
7 visits involving prescription opioids for each  
8 intent of use. The red box highlights that an  
9 estimated 50,000 ED visits in 2016 involved  
10 non-medical use of oxycodone, with non-medical use  
11 defined to include pharmaceutical abuse,  
12 therapeutic misuse, and overdoses without  
13 indication of intent.

14           This table highlights that among ED visits  
15 associated with non-medical use of oxycodone,  
16 approximately 40 percent or an estimated 22,000  
17 visits resulted in admission, transfer, or  
18 observation. As noted here, oxycodone was  
19 frequently adjusted with other agents, including  
20 prescription opioids, benzodiazepines, and most  
21 notably, illicit drugs or alcohol.

22           This graph shows the proportion of ED visits

1 associated with non-medical use of oxycodone that  
2 were associated with specific categories of adverse  
3 outcomes. Among the visits with non-medical use of  
4 oxycodone, nearly 20,000, resulted in patients  
5 experiencing a serious adverse outcome such as  
6 cardiac arrest, unresponsiveness, or respiratory  
7 failure and distress, collectively represented by  
8 the lighter blue section of this chart.

9 National data on drug-involved mortality  
10 were made available to the agency by the National  
11 Center for Health Statistics. Drug-involved  
12 mortality, DIM, combined the cause of death,  
13 demographic, and geographic information from the  
14 National Vital Statistics System Mortality, NVSS-M  
15 files, with information extracted from the death  
16 certificate literal text, allowing for more a  
17 granular analysis of specific drugs involved in  
18 deaths.

19 In this figure, we see the number of deaths  
20 involving various opioids over time. Included on  
21 this graph are oxycodone, the solid black line;  
22 hydrocodone, the lighter solid, brilliant gray

1 line; morphine, the darker dashed line; and heroin,  
2 the lighter dashed line.

3 Analysis of the NVSS-M and DIM linked  
4 databases found that in a 6-year period, from 2010  
5 to 2015, oxycodone involved deaths remained  
6 relatively unchanged with between approximately  
7 5[000] to 6,000 deaths per year. In contrast, a  
8 sharp increasing trend was observed for  
9 heroin-involved overdose deaths over the same time  
10 period, rising from approximately 3,000 in 2010 to  
11 over 13,000 deaths in 2015.

12 In summary, to review the data we've  
13 presented on misuse and abuse, with respect to  
14 scale, in 2016, 3.9 million individuals in the  
15 general population reported past year misuse of  
16 oxycodone-containing products defined by NSDUH to  
17 include both misuse and abuse. Greater than 3,000  
18 calls per year have been placed to poison control  
19 centers, reporting intentional exposure to  
20 oxycodone-containing products, and 35 percent of  
21 individuals entering treatment for opioid-use  
22 disorder reported past month abuse of

1       oxycodone-containing products. In terms of abuse  
2       of specific products, past month abuse of oxycodone  
3       IR products was more frequent than for oxycodone ER  
4       products. However, when adjusting for prescription  
5       volume, past month of use of oxycodone ER products  
6       appears to be more frequent.

7               For routes of abuse, abuse-deterrent ER/LA  
8       opioid analgesics are abused by multiple routes,  
9       where 60 percent of respondents in one study  
10       reported oral abuse, 20 to 30 percent reported  
11       abuse via snorting, while 30 percent reported abuse  
12       by injection. Finally, with morbidity and  
13       mortality, 40 percent of ED visits in 2016 that  
14       involved non-medical use of oxycodone-containing  
15       products required admission, hospitalization, or  
16       transfer. Nearly 20,000 ED visits with non-medical  
17       use of oxycodone-containing products involved  
18       patients experiencing serious adverse outcomes such  
19       as cardiac arrest or respiratory failure. Over the  
20       period of 2010 to 2015, over 30,000 deaths involved  
21       oxycodone.

22               Here, we highlight some key limitations of

1 the data sources we used, but these are described  
2 in more detail in the background information  
3 provided. NSDUH is affected by biases typical of  
4 most surveys, including recall response or social  
5 desirability bias. NPDS under-captures serious  
6 outcomes and may not provide a reliable picture of  
7 trends.

8 For the RADARS and NAVIPPRO systems, data on  
9 routes or patterns of abuse may not be nationally  
10 representative. This is a specialized population  
11 that's entering treatment. Additionally, product  
12 misclassification can occur as patients are  
13 identifying these products themselves through the  
14 surveys.

15 NEISS-CADES doesn't include cases that  
16 result in death before or during ED evaluation.  
17 This is certainly a limitation. There's also the  
18 potential for misclassification of products, which  
19 is done at the practitioner level. NEISS-CADES  
20 also only includes acute opioid harms resulting in  
21 ED visit. It doesn't include visits for opioid  
22 withdrawal, seeking treatment, detox, or inadequate

1 therapy, so it's sort of an underestimate of the  
2 true burden of morbidity. NVSS-M and DIM rely on  
3 the literal texts of the death certificate and are  
4 likely to miss the cases of drug-involved deaths  
5 where the drug is not listed on the certificate.

6 In conclusion, oxycodone-containing products  
7 are frequently dispensed in the U.S. with oxycodone  
8 ER products representing the majority of the ADF  
9 market. Oxycodone-containing products are the most  
10 frequently misused and abused prescription opioid  
11 products per population with high levels of abuse  
12 possibly driven by the wide utilization in the  
13 general population.

14 Products intended to deter abuse such as  
15 reformulated oxycodone ER are commonly abused by  
16 several routes, though most commonly oral followed  
17 by snorting and injection. And finally, despite  
18 the growing popularity of illicit opioids,  
19 oxycodone-containing products continue to be  
20 involved with high morbidity and mortality in the  
21 U.S.

22 Thank you. I want to acknowledge the other

1 members of the FDA review team who've all  
2 contributed substantially to the content presented  
3 today.

4 **FDA Presentation - Lisa Wiltrout**

5 DR. WILTROUT: Good morning. My name is  
6 Lisa Wiltrout. I'm a medical officer in the  
7 Division of Anesthesia, Analgesia, and Addiction  
8 Products. I'm going to provide you with a  
9 high-level, multidisciplinary review of the REMOXY  
10 ER new drug application. I will address the  
11 following in my presentation today, the  
12 aspirational goals for abuse deterrent opioid  
13 formulations, also known as ADFs; the current  
14 reality with ADFs; a brief summary of the clinical  
15 trial data and what data pertaining to abuse  
16 deterrence show; and lastly, FDA's approach to the  
17 evaluation of excipient safety with ADFs and what  
18 this means for REMOXY ER.

19 The goals for a successful ADF are twofold,  
20 consistent and effective delivery of an opioid dose  
21 when the ADF is used as labeled and either an  
22 expectation of or achievement of a reduction in

1 abuse by making the ADF more difficult to abuse by  
2 one or more relevant routes.

3 Goals are nice, but let's look at where we  
4 are today with ADFs. We know that ADFs are not  
5 abuse proof and do not prevent addiction. The FDA  
6 has approved 10 opioid analgesic products that are  
7 labeled with abuse-deterrent properties in  
8 accordance with the FDA guidance entitled, Abuse  
9 Deterrent Opioids: Evaluation and Labeling Guidance  
10 for Industry. Abuse-deterrent labeling is based on  
11 data from premarket studies. There are three  
12 categories of premarket studies, category 1, which  
13 are in vitro; category 2, which are  
14 pharmacokinetic; and category 3, which are clinical  
15 abuse-potential studies.

16 Abuse-deterrent labeling is located in  
17 section 9.2 of the prescribing information. All  
18 approved ADFs have postmarketing requirements to  
19 conduct additional category 4 studies. As stated  
20 in the FDA guidance, the goal of postmarket studies  
21 is to determine whether the marketing of a product  
22 with abuse-deterrence properties results in

1 meaningful reductions in abuse, misuse, and related  
2 adverse clinical outcomes, including addiction,  
3 overdose, and death in the post-approval setting.

4 Published studies evaluating ADFs in the  
5 post-approval setting exists, however, to date, no  
6 postmarket data have been submitted to the FDA that  
7 support a meaningful effect of ADFs on reductions  
8 in abuse and misuse in the community.

9 The applicant has met the evidentiary  
10 standards for a reformulated opioid analgesic. The  
11 applicant used the 505(b)(2) pathway referencing  
12 Roxicodone, which is an immediate-release  
13 oxycodone-containing drug product. We required the  
14 applicant to conduct one adequate and  
15 well-controlled phase 3 clinical trial to support  
16 the efficacy of REMOXY ER given the change in  
17 dosing interval from every 4 to 6 hours for an  
18 immediate-release product to twice a day for an  
19 extended-release product.

20 Study PTI-821-CO, described earlier by the  
21 applicant, was conducted under special protocol and  
22 provided substantial evidence of efficacy for the

1 proposed indication. We required additional  
2 clinical data to support the safety of REMOXY ER  
3 given that it is a reformulation of oxycodone. The  
4 applicant conducted a second phase 3 clinical  
5 trial, study PTI-821-CM, to support the long-term  
6 safety of REMOXY ER. In the available clinical  
7 trial data, REMOXY ER has an adverse event profile  
8 typical of an extended-release opioid.

9 Now, I will summarize the abuse-deterrence  
10 findings with REMOXY ER by route of abuse. As  
11 discussed earlier by Dr. Tolliver, the oral human  
12 abuse potential study fails to demonstrate an  
13 effect on abuse deterrence. Additionally, in vitro  
14 data demonstrate that oxycodone, suitable for oral  
15 abuse, can be extracted from REMOXY ER using  
16 manipulation method RM10 in study conditions  
17 solvent S1, volume D, and temperature F.

18 As discussed earlier by the applicant, the  
19 intranasal human abuse potential study meets  
20 current standards for intranasal abuse-deterrent  
21 labeling. Subjects in this study experience less  
22 drug liking and less willingness to take drug again

1 with REMOXY ER than with the immediate-release  
2 comparator under the conditions tested. Based on  
3 an analysis of available epidemiological and  
4 in vitro data, we do not consider smoking a  
5 relevant route of abuse for oxycodone.

6 As I will discuss in more detail on the  
7 following slide, category 1 studies conducted by  
8 the FDA lab generated results that were different  
9 than those presented by the applicant. The  
10 clinical implications of these results are  
11 concerning. The FDA lab performed a set of  
12 manipulations and extractions using the same  
13 conditions as those described by the applicant to  
14 replicate some of the applicant's category 1 data.  
15 In the next two slides, I will summarize the most  
16 relevant results.

17 The table presented here shows that up to 72  
18 percent of oxycodone content was extracted from  
19 REMOXY ER with no pretreatment using manipulation  
20 method RM11 in study conditions solvent S20,  
21 volume b, time H. A relatively simple process  
22 yielded as much as 15 milligrams of oxycodone. And

1 the table on this slide shows that more oxycodone  
2 content, up to 83 percent, was extracted from  
3 REMOXY ER with pretreatment C and temperature G,  
4 again using manipulation method RM11 in study  
5 conditions solvent S20, volume B, and time H. A  
6 slightly more involved process that is not beyond  
7 the scope of an experienced IV drug user yielded as  
8 much as 29 milligrams of oxycodone that was  
9 syringeable.

10 We recognize that there are limitations to  
11 category 1 studies. There are many variables at  
12 play, and the methodology used in these studies is  
13 not standardized. Nevertheless, the take-home  
14 message is that fairly basic manipulation and  
15 extraction methods generated high yields of  
16 oxycodone suitable for injection. Moreover, these  
17 manipulation and extraction methods are presumed to  
18 be readily available in the community.

19 The implications of the FDA lab findings are  
20 clear. Oxycodone suitable for IV use can be  
21 extracted from REMOXY ER. The amount of extracted  
22 oxycodone and the extraction volume may lead to

1 sharing among IV drug users. Given what happened  
2 with Opana ER, other important public health  
3 consequences are to be expected.

4 The previous slides show some troubling data  
5 from the limited perspective of oxycodone available  
6 for injection following extraction. Drawing on our  
7 experience with Opana ER, it is necessary to  
8 discuss the unintended consequences of excipients  
9 when manipulated and administered by an unintended  
10 route. We routinely require an adequate assessment  
11 of excipient safety for the intended route or  
12 routes of administration.

13 We have a guidance entitled FDA Guidance for  
14 Industry: Nonclinical Studies for the Safety  
15 Evaluation of Pharmaceutical Excipients. Prior to  
16 certain key events, we did not require any  
17 assessment of excipient safety for oral drug  
18 products being abused by the IV route or other  
19 unintended routes.

20 ADF opioid development and use has presented  
21 a learning experience for both FDA and industry.  
22 Postmarket experience with ADFs has yielded some

1 unanticipated outcomes when ADFs are abused by  
2 unintended routes. Based on the available data,  
3 parallels can be drawn between Opana ER and REMOXY  
4 ER. Opana ER, much like REMOXY ER, showed some  
5 abuse deterrence by the nasal route.

6 In the case of Opana ER, data suggest that  
7 persons abusing the drug shifted from one route of  
8 abuse, nasal, to another more dangerous route of  
9 abuse, injection. This shift from non-parenteral  
10 to parenteral use of Opana ER was consequential.

11 Some IV drug users experienced thrombotic  
12 microangiopathy with IV use of manipulated  
13 Opana ER, which an investigation showed was due to  
14 injection of the PEO excipient. Additionally, the  
15 method used for preparation of Opana ER for  
16 injection resulted in a solution that could be  
17 shared. We saw an increase in transmission of  
18 blood-borne diseases, HIV and hepatitis C, in IV  
19 drug users who were sharing manipulated Opana ER.

20 Not all of the parallels between Opana ER  
21 and what we currently know about REMOXY ER are  
22 directly related to the excipients. However, given

1 the thrombotic microangiopathy and PEO experience  
2 with Opana ER, the FDA is now much more interested  
3 in understanding the potential risks associated  
4 with IV exposure and exposure by other unintended  
5 route to excipients in oral drug products.

6 We require sponsors to submit a safety  
7 assessment of the potential adverse effects  
8 associated with abuse of the final drug product.  
9 The safety assessment is needed to determine the  
10 complete risk-benefit profile of the drug, and we  
11 included potential excipient related adverse  
12 effects from abuse of ADFs in section 9.2 of the  
13 label.

14 The applicant has already provided a review  
15 of their approach to assessing excipients safety  
16 with potential IV abuse of REMOXY ER. We note the  
17 following limitations of the applicant's safety  
18 assessment. The applicant only looked for known  
19 REMOXY ER excipients and the expected degradants.  
20 The extraction conditions employed were basic  
21 typical forms of manipulation.

22 The IV abuse simulation conditions that

1 yielded the largest amount of extracted oxycodone,  
2 termed the worst case IV abuse simulation  
3 conditions by the applicant, were not employed in  
4 the excipient safety assessment. Therefore,  
5 excipient safety utilizing the conditions most  
6 likely to be replicated by a person seeking to  
7 manipulate REMOXY ER, extract oxycodone, and inject  
8 it remains unknown. It is also important to  
9 remember for all ADFs, that we cannot predict  
10 everything that could happen with the drug product  
11 once it is marketed. Case in point is Opana ER.

12 In summary, the applicant's data support the  
13 safety and efficacy of REMOXY ER as an  
14 extended-release, long-acting opioid analgesic for  
15 the proposed indication. The applicant's  
16 abuse-deterrence data for REMOXY ER meet current  
17 standards for abuse-deterrent labeling by the nasal  
18 route. However, the abuse-deterrence data do not  
19 meet the current standards for abuse-deterrent  
20 labeling by the oral route. We generally do not  
21 consider smoking a relevant route of abuse for  
22 oxycodone based on an analysis of available

1 epidemiological and in vitro data.

2 Results of category 1 studies conducted by  
3 the FDA lab demonstrate that oxycodone suitable for  
4 IV use can be extracted from REMOXY ER under  
5 certain conditions. Given this information about  
6 REMOXY ER's vulnerability to manipulation and abuse  
7 by the IV route under specific conditions, the  
8 applicant safety assessment of excipient risks from  
9 abuse of the final drug product is incomplete.  
10 Thank you.

11 **Clarifying Questions**

12 DR. McCANN: Are there any clarifying  
13 questions for the FDA or the speaker? Please  
14 remember to state your name for the record before  
15 you speak. If you can, please direct questions to  
16 a specific presenter. Dr. Goudra?

17 DR. GOUDRA: Dr. Goudra from pain medicine.  
18 Maybe this question was answered by Dr. Lisa  
19 Wiltrout. How common and how relevant is drug  
20 manipulation used as insufflation or inhalational  
21 purposes? Is it really that big of a problem in  
22 the country?

1 DR. WILTROUT: I'm sorry. Could you repeat  
2 the question for me?

3 DR. GOUDRA: Yes. How relevant is the  
4 problem of drug manipulation for the purposes of  
5 nasal insufflation or inhalation, or smoking or  
6 nasal use?

7 DR. WILTROUT: I'll defer that to Dr. Hertz.

8 DR. STAFFA: This is Judy Staffa. I think  
9 in Dr. Mundkur's presentation, you saw that it was  
10 around 30-ish percent of how people are abusing  
11 this, that they would have to manipulate it in  
12 order to then be able to snort it.

13 DR. GOUDRA: I guess my question was  
14 slightly different.

15 DR. STAFFA: Okay. Then we're not  
16 understanding it. My apologies.

17 DR. GOUDRA: In terms of the number deaths  
18 that have occurred in the USA, so 19,000 or  
19 something, how common have people used the drugs in  
20 alternate route? Was it, say, overdosing by oral,  
21 or intravenous, or something like that?

22 DR. STAFFA: Thank you for clarifying your

1 question. Those kinds of data are not easily  
2 obtained.

3 DR. GOUDRA: Okay. Thank you.

4 Sorry. In fact, I have another question.  
5 In terms of the REMOXY data that's presented, is  
6 there anything anybody can do or take -- I'm not  
7 mentioning the excipients, which are already there.  
8 Can somebody manipulate the pH in the stomach or  
9 intestine by taking something else to influence the  
10 drug absorption and increase the pharmacodynamic  
11 availability?

12 DR. HERTZ: This is Sharon Hertz. We only  
13 have data on methods that were described during the  
14 closed session. Other standard evaluations include  
15 food effect, so we do have data on that. We didn't  
16 present because we don't always present things that  
17 don't raise questions. So we didn't have a concern  
18 that, for instance in this case, the food effect  
19 altered absorption in a meaningful way. But we  
20 don't have anything else other than what you saw  
21 this morning.

22 DR. McCANN: Dr. Zeltzer, please?

1 DR. ZELTZER: Thank you. Lonnie Zeltzer,  
2 UCLA. So one of the issues in terms of differences  
3 between FDA findings and the pharmaceutical  
4 company's findings have to do with certainly risks  
5 for manipulation for IV administration, with all  
6 the downstream potential consequences of making a  
7 drug -- another drug entering the market able to go  
8 the IV route. And the company's data talked about  
9 the complications because of viscosity and other  
10 characteristics that made it so difficult for IV  
11 administration.

12 I don't know who to ask to sort of explain  
13 some of the differences.

14 DR. HERTZ: This is Sharon Hertz. I'll  
15 start. When we do the in vitro studies to evaluate  
16 the ability to manipulate for the purpose of  
17 intravenous abuse, there are a series of different  
18 types of manipulation. We ask for the most direct  
19 approach of getting drug into syringe, and those  
20 are the syringeability or injectability studies.  
21 And those are the studies that were described by  
22 the sponsor, where they just couldn't do that,

1 based on the nature of the material.

2           Then we look at small-volume extraction.  
3 Within the in vitro manipulations, we do a variety  
4 of things because, as the sponsor said, we ask them  
5 to keep pushing until they defeat the product.  
6 It's not a surprise that all products have some  
7 ability to be defeated because if you couldn't get  
8 the drug out of them, well, what good are they? So  
9 it's a progressive approach to see how far one  
10 needs to go.

11           The trouble is the data available -- and  
12 I'll use our quotes. "The data available on  
13 manipulation is not a static text." What we know  
14 is that -- well, we learned a lot of this with  
15 Opana, is that individuals who have a particular  
16 product available to them will do what they can to  
17 attempt to defeat that product. So what happened  
18 with Opana was surprising, the methods that were  
19 used, the combination of conditions, the results  
20 that differed by location. So it's not even as if  
21 one can assume the same methods to get the drug out  
22 will be the same across the country.

1           So we have laid out in guidance, and through  
2 discussions with the agency, we asked for a variety  
3 of things. The sponsor conducted them. And then  
4 the difference, the big difference is that even  
5 using some of the same categories, the same types  
6 of manipulations, our lab yielded more. And like I  
7 had mentioned, this is a phenomenon that we know  
8 about.

9           With chemistry method standardization is  
10 quite important because there are a large number of  
11 variables that can impact the outcome. And part of  
12 the reason why our labs do studies is to understand  
13 the formulations better, as well as to see how the  
14 results compare.

15           So that's really where the difference is.  
16 It's not the injectability or syringeability, but  
17 the ability to extract the oxycodone from the  
18 product using a variety of conditions that you  
19 heard about this morning.

20           DR. McCANN: Ms. Griffin? Dr. Griffin?  
21 Sorry.

22           DR. GRIFFIN: Marie Griffin. I'm wondering

1 if you could take that one step further. So if you  
2 can extract it, then should there be injectability  
3 studies of that extracted material, or is that  
4 possible to do further studies?

5 DR. HERTZ: Traditionally once extracted,  
6 it's going to be in a liquid form, so we don't  
7 usually have concerns about the viscosity. Now, it  
8 may have a lot of nasty material accompanying the  
9 oxycodone, which is why we've been adding these  
10 evaluations of what comes out, again, having been  
11 finding out about problems with other products  
12 along the way. So it's been a learning experience  
13 for us, for industry, as more and more products  
14 are evaluated, and then we see what actually  
15 happens.

16 We can't possibly anticipate all the  
17 conditions that will be attempted by the community  
18 seeking to abuse these products by different  
19 methods. We ask for a lot, but there are  
20 limitations. So the idea behind it, if we take a  
21 few steps back, these products are trying to deter  
22 so that if somebody decides they want to abuse it,

1 there are obstacles in their way for readily  
2 manipulating the product to do what ER products can  
3 do, which is dose dump under certain conditions  
4 readily; so starting from no resistance and then  
5 how much can these attempts be forced to escalate  
6 in effort and sophistication.

7 DR. McCANN: So we're fortunate that the  
8 real chairman of this committee, Raeford Brown, I  
9 understand is online and wants to communicate with  
10 the group. So I would ask him to introduce  
11 himself, and then make his comments.

12 (No response.)

13 DR. McCANN: Maybe he's not online. Right?  
14 All right. We're going to go to our next person,  
15 Dr. Goudra.

16 DR. GOUDRA: Dr. Goudra from pain medicine.  
17 This question concerns the only study, which is  
18 PTI-082-10. I'm just curious to know why did you  
19 guys choose patients with osteoarthritis or  
20 [indiscernible] knee. It's I don't think a typical  
21 case where patients use opioids. Those patients  
22 have surgical options for these. And low back pain

1 probably is [indiscernible].

2 DR. McCANN: I think we're still doing FDA  
3 questions, Dr. Goudra.

4 DR. GOUDRA: Okay.

5 DR. McCANN: We're still at the FDA part.  
6 Sorry.

7 Are there any questions left for the FDA?

8 (No response.)

9 DR. McCANN: Then we will go on to the  
10 sponsor and Dr. Goudra's question.

11 DR. FRIEDMANN: There are a lot of pain  
12 models for acute pain, but not a lot of pain models  
13 for chronic pain. Normally you use either low-back  
14 pain or osteoarthritis? At the time we did the  
15 study, these were the classical models. That's why  
16 we used one of them.

17 DR. McCANN: I had a question for the  
18 sponsor. Mary Ellen McCann. My question  
19 was -- and maybe this gets to what Sharon was  
20 saying a little bit earlier. But in my experience  
21 as a pediatric anesthesiologist trying to get med  
22 sedatives into young children that have neither and

1 IV or unwilling to swallow a medication, we often  
2 give these medicines sublingually or intranasally  
3 but not snorting. When I first looked at this  
4 medication, my inclination was if I had a  
5 medication that was like super thick Vaseline, why  
6 don't I just put it on my finger and smear into my  
7 buccal mucosa and see what happens.

8 Did anybody at your company try that?

9 DR. FRIEDMANN: Somebody in the company  
10 tried the placebo into their nose. But as you have  
11 seen, we have done the nasal study, and you don't  
12 get the blood levels. So why would you want to do  
13 that?

14 DR. McCANN: But the nasal study was trying  
15 to basically make it into particulate and then sort  
16 of blow it in --

17 DR. FRIEDMANN: No, no. There were two.  
18 One was manipulated REMOXY and one was REMOXY  
19 intact, and neither one provided any significant  
20 levels.

21 DR. McCANN: Thank you.

22 So our next question is Dr. Brent.

1 DR. BRENT: Thank you Jeffrey Brent here. I  
2 have a question for Dr. Friedmann, and it is about  
3 your phase 3 efficacy study. Just so we fully  
4 understand the design of the study, were your  
5 patients who had chronic osteoarthritic knee pain  
6 using opioids before they were enrolled in the  
7 study?

8 DR. FRIEDMANN: Yes, they were.

9 DR. BRENT: And they were then withdrawn  
10 from their opioids, the washout period.

11 DR. FRIEDMANN: That is correct.

12 DR. BRENT: So basically all the patients  
13 had to go through a period of opioid withdrawal  
14 before being put on --

15 DR. FRIEDMANN: No. That isn't correct.  
16 Not all patients were on opioids before they  
17 started this study. Some were opioid naive. So  
18 the starting dose of the study for those that were  
19 naive was the 5 milligrams.

20 DR. BRENT: Right.

21 DR. FRIEDMANN: Patients who were at the  
22 higher dose initially, they were given equivalent

1 dose of oxycodone.

2 DR. BRENT: Equivalent dose.

3 DR. FRIEDMANN: Yes.

4 DR. BRENT: So the study population was a  
5 mixed population of opioid-dependent and opioid-  
6 naive patients?

7 DR. FRIEDMANN: That is correct.

8 DR. BRENT: Okay. And then when they went  
9 through the protocol, you then went through a  
10 tapering period at the end of the study?

11 DR. FRIEDMANN: Yes.

12 DR. BRENT: What percentage of the patients  
13 during that time went through withdrawal?

14 DR. FRIEDMANN: I do not have this. I don't  
15 think very many. The withdrawal period was based  
16 on the presumed dose -- since it was blinded, we  
17 don't know what dose they were, so we way to assume  
18 those a particular dose that they were on. And  
19 based on that, the number of days they were  
20 withdrawn varied. But I do not recall many people  
21 in withdrawal.

22 DR. BRENT: So you had people that were

1 receiving -- what was the maximum dose that was  
2 given? Was it the 40-milligram dose?

3 DR. FRIEDMANN: Yes.

4 DR. BRENT: Right. So you had people that  
5 were given the 40-milligram dose for 12 weeks, and  
6 then when you stopped it, you say you don't believe  
7 they had withdrawal?

8 DR. FRIEDMANN: No. They were tapered down  
9 over 2 weeks blindly.

10 DR. BRENT: Right. Okay. Yes.

11 DR. FRIEDMANN: So if they were on 40, they  
12 went to 30, to 50, and I forget the exact numbers,  
13 then to 5.

14 DR. BRENT: Okay. And you don't think they  
15 withdrawal symptoms?

16 DR. FRIEDMANN: I don't recall any.

17 DR. BRENT: Okay. Thank you.

18 DR. McCANN: Dr. Hertig?

19 DR. HERTIG: John Hertig, Purdue University.

20 My question is for Dr. Marsman related to the  
21 postmarketing safety initiatives. One of the  
22 initiatives mentioned is drug disposal, and as many

1 of us know, still the biggest route of abuse is  
2 oral, especially with diverted medications. So  
3 drug disposal becomes a really important issue.

4 Can you talk to me just a little bit about  
5 what the plan drug disposal program is and how it  
6 may work with current disposal technologies that  
7 are available that are designed to sequester  
8 medications?

9 DR. MARSMAN: Yes. We're still in the  
10 process of exploring that. We're starting to talk  
11 to distributors and third-party vendors to try  
12 to -- and this is a discussion that also goes on  
13 with some members of the REMS consortium as well,  
14 to try to find the best mechanism to do this. I  
15 don't have details to give you now because we're in  
16 a preliminary research of looking at this.

17 DR. HERTIG: Thank you.

18 DR. McCANN: Dr. Terman?

19 DR. TERMAN: Sure. It sounds like most of  
20 the questions I had have been asked. I will  
21 clarify, the irritant smoking, that's theoretical,  
22 right? There's no data from the company.

1 DR. FRIEDMANN: That's correct.

2 DR. TERMAN: The phase 3 was very  
3 interesting to me. Did you look at any of the  
4 outcome measures except at the end? Did you look  
5 at them after randomization, for instance, to see  
6 whether there were differences between groups?

7 DR. FRIEDMANN: In terms of what?

8 DR. TERMAN: Pain, function. Were there any  
9 differences before -- when you randomized and  
10 before you started to taper the placebo, were there  
11 any differences between the groups at that state?

12 DR. FRIEDMANN: Before we randomized, there  
13 were no differences because that's how we  
14 randomized them. We randomize not only -- by pain  
15 scores twice at the beginning of the study and then  
16 at the randomization. So when we randomized, the  
17 high pain scores were randomized into one group and  
18 the low pain scores were into one group. So that's  
19 the best we could do on the randomization.

20 DR. TERMAN: But that doesn't really answer  
21 the question of when you finished randomizing,  
22 whether there were differences between the groups.

1 I mean, yes, higher.

2 DR. FRIEDMANN: I don't think we looked into  
3 it.

4 DR. TERMAN: Okay. The other question of  
5 course would be what happened to the pain scores or  
6 function in the people that you tapered down? That  
7 would be useful information as well, but you didn't  
8 look at that.

9 DR. FRIEDMANN: No, it was not done.

10 DR. TERMAN: So mostly all of those outcome  
11 measures were at the very end of the studies.

12 DR. FRIEDMANN: You're right, at the end of  
13 the study. That's correct.

14 DR. TERMAN: Okay. And I'm not sure whether  
15 FDA or you would be best to ask this question. Do  
16 you know whether OxyContin has been looked at in  
17 terms of the 5-minute chewing sort of approach? It  
18 wasn't in the OxyContin information that was given  
19 to us. A study like that wasn't done as far as I  
20 can tell.

21 DR. FRIEDMANN: I do not know that -- would  
22 you like to answer that

1 DR. HERTZ: This is Sharon Hertz. We took  
2 all that to advisory committee a long time ago, and  
3 there were chewing studies and there were other  
4 studies for oral route of abuse, and they did not  
5 succeed in getting a labeling claim. So the  
6 studies were not able to meet the criteria for  
7 success from an oral deterrent effect.

8 DR. TERMAN: Okay. So hard to know how that  
9 would look in comparison to the chewing failure  
10 here as far as I'm concerned, so failure --

11 DR. FRIEDMANN: Well, I don't think it's a  
12 failure on REMOXY because if you look at the blood  
13 level, on REMOXY, it was 65.9 nanograms per mL.  
14 Xtampza intact is over 62 nanograms per mL. So  
15 REMOXY chewed compared to Xtampza intact, it's  
16 about the same level.

17 I think the failure in that study was the  
18 failure of the immediate release. The immediate  
19 release was 75 nanograms per mL. This is one of  
20 the lowest numbers that I have seen in many studies  
21 that I reviewed on immediate release. Xtampza,  
22 when they presented to the committee, study number

1 17, the IR was 116 nanograms per mL. If we had 80  
2 nanograms, we would have been significantly  
3 different than they the IR.

4 DR. TERMAN: Okay. But it certainly appears  
5 on page 48 that there was a significant difference.  
6 I don't know how clinically significant, but in  
7 terms of your chewed and unchewed product --

8 DR. FRIEDMANN: Clearly.

9 DR. TERMAN: -- there was a very big  
10 difference.

11 DR. FRIEDMANN: No question, yes.

12 DR. TERMAN: And that can cause some  
13 concerns if that's the way abuse is taking place.

14 One last question. Apart from the smaller  
15 dose, which is a difference from other products on  
16 the market, what would you say is the benefit?  
17 Apart from the abuse deterrent issue, what would  
18 you say is the advantage of this product?

19 DR. FRIEDMANN: Oxycodone is oxycodone, so  
20 it's going to be better. It's really the  
21 formulation. We presented category 1 data much  
22 better -- that REMOXY performed much better than

1 the immediate release, or OxyContin, Xtampza, that  
2 can be defeated very quickly at 80 or 95 percent.  
3 The FDA presented data on REMOXY, but they did not  
4 present data on the comparator on the same  
5 conditions. So it's hard for us to judge what  
6 really happened in that regard.

7 DR. McCANN: I understand Dr. Raeford Brown  
8 is now on the line. We'll give him a second try.

9 DR. FRIEDMANN: Wait. I didn't finish. I  
10 didn't finish the question.

11 So the formulation is one thing. The other  
12 thing is the PK data. REMOXY PK data is very  
13 different -- we have a slide for that if you'd like  
14 to see it. It's very different. The PK and the  
15 steady-state kinetics are very different for REMOXY  
16 than the other products.

17 The steady-state state kinetics for REMOXY  
18 is 66 nanogram per mL. The steady-state kinetics  
19 for Xtampza and OxyContin is 76. The minimum  
20 effect for both of them is around 20 nanogram per  
21 mL. For REMOXY it's 25. So they've peak to trough  
22 fluctuation is about 50 percent different; not

1 quite, but just about 50 percent between REMOXY and  
2 the other two products.

3 DR. TERMAN: Okay. Thank you.

4 DR. McCANN: I think we're done with that  
5 question.

6 DR. FRIEDMANN: Okay.

7 DR. McCANN: We're going to go on and give  
8 Dr. Brown a third try.

9 DR. BROWN: Hi. This is Rae Brown, and I am  
10 a professor of anesthesiology and pediatrics at the  
11 University of Kentucky. This has been a very  
12 interesting conversation, and I have question for  
13 the FDA. And it relates to the formulation of  
14 REMOXY relative to the agents that were tested by  
15 the sponsor but not tested by the FDA. The medical  
16 officers presented some very good data that  
17 suggested that all oxycodone formulations are  
18 problematic, and one wonders whether or not this  
19 directs us to look more closely at the safety of  
20 oxycodone on the market.

21 DR. HERTZ: This is Sharon Hertz.

22 DR. BROWN: That question is for the FDA.

1 DR. HERTZ: Hi Rae. This is Sharon Hertz.  
2 I didn't quite catch the full question. I believe  
3 you referenced the in vitro data that we had, and  
4 what is the question based on that?

5 DR. BROWN: The medical officers presented  
6 data about the relative risk of having oxycodone in  
7 general on the market, whether it be in any ADF  
8 formulation. So my question is, does the FDA feel  
9 like there is sufficient evidence to warrant  
10 putting another ADF oxycodone on the market?

11 DR. HERTZ: I believe the question  
12 is -- just to sort of paraphrase and make sure that  
13 I've got this right -- we presented -- this was  
14 actually our epidemiology group, presented data on  
15 the current availability of oxycodone products on  
16 the market, including the ADF products, and are  
17 there data to support putting another ADF on the  
18 market or this ADF on the market?

19 Was your question specific to this or in  
20 general?

21 DR. BROWN: Well, it's really a question in  
22 general, but since we're talking about this ADF,

1 it's an opportunity to raise the question.

2 DR. HERTZ: Okay. I'm not going to answer  
3 the specific question because that's what we're  
4 going to ask you guys to vote on. But in terms of  
5 general, if we ask the question, how many versions  
6 of a product are appropriate to be on the market, I  
7 would say the answer is as many as meet adequate  
8 criteria for marketing.

9 We don't have a limit on how many  
10 abuse-deterrent formulations of a particular drug  
11 substance should be marketed at any one time. So  
12 going back something I mentioned in my introductory  
13 comments, there is concern that the approval of new  
14 products might expand the market, might expand the  
15 use of opioids. And it's sort of a subtext kind of  
16 question in terms of how many ADFs should be on the  
17 market of any given product.

18 This was published in Anesthesiology. Was  
19 it 2017 or 2018? 2017, and we can put the citation  
20 somewhere for folks to get.

21 (Crosstalk.)

22 DR. HERTZ: Oh, there you go. It's in our

1 backgrounder. So the availability of opioid  
2 analgesics is not currently limited by the products  
3 available. The amount on the market is based on  
4 the number of prescriptions being filled. So with  
5 new approvals, what we found was the number of  
6 approvals, both innovator and generic -- and there  
7 are many more generic approvals than innovators.  
8 If you look at that over time and then you look at  
9 the number of prescriptions over time, they  
10 intersect, meaning the -- well, of course,  
11 depending on scale. But they have opposite slopes.

12 The number of new products, new innovators,  
13 new generics, is rising, is increasing. The number  
14 of opioid prescriptions is decreasing over that  
15 same time period. So we don't limit the number of  
16 a given kind of drug. What we try to do is create  
17 a standard for them. And then if products start to  
18 exhibit differences in efficacy or safety, we look  
19 at that in the context of public health, relative  
20 risk, that sort of thing, which of course are all  
21 very difficult to measure or quantitate.

22 DR. BROWN: Sharon, I appreciate that.

1       However, this is not a single variable issue, and  
2       the problem with the paper that you presented to us  
3       in the backgrounder is that it appears to presume  
4       that this is a single variable issue, and that is  
5       that the only variable is the increase in the  
6       number of ADFs on the market and the decrease in  
7       the number of prescriptions. I won't push this any  
8       further, but I think it's food for thought in your  
9       deliberations after this meeting.

10               DR. HERTZ: This is Sharon Hertz. Thank you  
11       for that. Rae. I'm sure we'll have some  
12       conversations about that.

13               DR. McCANN: With that, we have three or  
14       four more comments, but I'm afraid of bumping into  
15       the open public hearing. So we're going to adjourn  
16       for lunch and get to the comments after the open  
17       public hearing.

18               I would like to say we will reconvene here  
19       at 1:30 p.m. Please take any personal belongings  
20       you may want with you at this time. Committee  
21       members, please remember that there should be no  
22       discussion of the meeting during lunch amongst

1       yourself, with the press, or with any other members  
2       of the audience. Thank you.

3                       (Whereupon, at 12:42 p.m., a lunch recess  
4       was taken.)

5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

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

(12:42 p.m.)

**Open Public Hearing**

DR. McCANN: We're going to begin the open public hearing session.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement

1 to advise the committee if you do not have any such  
2 financial relationships. If you choose not to  
3 address this issue of financial relationships at  
4 the beginning of your statement, it will not  
5 preclude you from speaking.

6 The FDA and this committee place great  
7 importance on the open public hearing process. The  
8 insights and comments provided can help the agency  
9 and this committee in their consideration of the  
10 issues before them. That said, in many instances  
11 and for many topics, there will be a variety of  
12 opinions. One of our goals today is for this open  
13 public hearing to be conducted in a fair and open  
14 way where every participant is listened to  
15 carefully and treated with dignity, courtesy, and  
16 respect. Therefore, please speak only one  
17 recognized by the chairperson. Thank you for your  
18 cooperation.

19 Will speaker number 1 step up to the podium  
20 and introduce yourself? Please state your name and  
21 any organization you are representing for the  
22 record.

1 DR. POLANIN: Thank you for the opportunity  
2 to speak today on behalf of the National Center for  
3 Health Research. I am Dr. Megan Polanin. Our  
4 research center analyzes scientific and medical  
5 data and provides objective health information to  
6 patients, providers, and policymakers. We do not  
7 accept funding from industry, so I have no  
8 conflicts of interest.

9 We strongly support the FDA's efforts to  
10 encourage the development of opioid analgesics that  
11 deter abuse. As with any other drug, the FDA  
12 evaluates these opioids should be held to a high  
13 standard for approval to maximize the probability  
14 that the risk of abuse is actually lower than it  
15 would be without properties designed to deter  
16 abuse.

17 We all know that oxycodone is one of the  
18 most highly abused opioids. For example, from 2012  
19 to 2016 calls to poison control centers indicated  
20 that intentional abuse of oxycodone was only  
21 surpassed by heroin. RADARS and NAVIPPRO databases  
22 both found that oxycodone was the second most

1 highly abused opioid. In addition, oxycodone was  
2 the second most commonly reported abused drug among  
3 patients entering treatment for opioid-use  
4 disorder.

5           With this context in mind, please consider  
6 these two questions as you evaluate REMOXY's  
7 patient and public health benefit-risk ratio. Has  
8 the sponsor shown that REMOXY has properties that  
9 will deter abuse by oral, nasal, and intravenous  
10 routes of administration? If REMOXY can prevent  
11 abuse through all three known routes of abuse, that  
12 would be a very positive step for preventing  
13 further misuse and abuse and initiate a higher  
14 standard for abuse deterrent drugs.

15           That is not the case with this drug.  
16 Category 1 studies showed that REMOXY's physical  
17 properties successfully deterred abuse via  
18 injection, snorting, and smoking. Human potential  
19 abuse studies indicated that REMOXY might deter  
20 intranasal abuse. For example, when compared with  
21 oxycodone IR, REMOXY was more difficult to use  
22 intranasally and less likable for abusers.

1           However, we're concerned that results from  
2 the oral human abuse potential study showed that  
3 chewed REMOXY did not deter abuse compared with  
4 crushed oxycodone IR tablets for half of the  
5 primary endpoints. And as the FDA stated, the  
6 significant findings may not be clinically  
7 relevant. In addition, the FDA's category 1  
8 studies showed that oxycodone can in fact be  
9 extracted from REMOXY. Finally, excipient risks  
10 have not yet been adequately tested.

11           It is well known that abusers of the drug  
12 can be very creative in finding unique ways to  
13 overcome deterrence. Because oxycodone is a highly  
14 abused drug, we are concerned that this drug could  
15 still be abused orally and intravenously.

16           Finally, we want to point out that REMOXY  
17 was compared with oxycodone and oxycodone IR drug  
18 and not compared with current abuse-deterrent  
19 oxycodone ER/LA products on the market. What are  
20 the potential unintended harms of REMOXY in the  
21 real world? We know that patients continue to  
22 abuse ER/LA oxycodone with abuse-deterrent

1 formulations and that oxycodone ER tablets are  
2 particularly vulnerable for abuse.

3 In the laboratory setting, REMOXY appears to  
4 meet the FDA's current standards for determining  
5 intranasal and intravenous abuse. Whether its  
6 abuse-deterrent properties are effective in the  
7 real world is a much more difficult question that  
8 will require postmarketing data. We know from  
9 previous experience that so-called abuse-deterrent  
10 opioids are sometimes abused more widely than  
11 current laboratory studies suggest. Opana ER is  
12 one example.

13 To reduce the opioid epidemic, the FDA must  
14 hold pharmaceutical companies to a high and  
15 truthful standard. REMOXY did not meet the FDA  
16 standards for oral abuse, and it may be able to be  
17 abused intravenously. The safety of the excipient  
18 is also in question. Please carefully consider the  
19 risks of putting another drug with abuse-deterrent  
20 labeling on the market that could  
21 result in misuse and abuse in the real world. We  
22 urge this advisory committee to vote that the

1 benefits of this drug do not outweigh its potential  
2 risks. Thank you for the opportunity to share our  
3 perspective.

4 DR. McCANN: Will speaker number 2 step up  
5 to the podium and introduce yourself? Please state  
6 your name and any organization you are representing  
7 for the record.

8 MR. THOMPSON: Good afternoon. I'm Edwin  
9 Thompson, president of Pharmaceutical Manufacturing  
10 Research Services. For full disclosure, I have  
11 submitted all supporting documents from this  
12 presentation to the FDA docket. They are publicly  
13 available.

14 2016 and 2017 are the first two consecutive  
15 years, since the flu epidemic in 1925, that life  
16 expectancy in the United States has declined,  
17 driven by the opioid epidemic. The opioid epidemic  
18 is an iatrogenic and preventable. But the FDA's  
19 solutions offered do not identify or address the  
20 root cause.

21 The United States opioid epidemic is in its  
22 23rd consecutive year with an increasing number of

1 deaths each year. The root cause of the opioid  
2 epidemic is the illegal FDA approval of opioids for  
3 the treatment of chronic pain. FDA is asking this  
4 committee for a recommendation on your  
5 approvability of REMOXY. You're being asked to  
6 continue to fuel this epidemic. The answer is  
7 unquestionably no. Your individual vote and  
8 committee recommendation will tell us if you're the  
9 clean-up committee or the cover-up committee.

10 REMOXY has been submitted as a 505(b)(2)  
11 product, relying on the data submitted in the 1995  
12 OxyContin FDA approval. Your vote today will  
13 either affirm or reject the OxyContin data.

14 This slide is the FDA cover sheet for the  
15 integrated summary of efficacy for OxyContin,  
16 completed in June 1995 by Dr. Curtis Wright and  
17 reviewed by Dr. Douglas Kramer. There were 6  
18 double-blind studies, only 2 of which are placebo  
19 controlled. The FDA approved OxyContin on a single  
20 one study, adequate and well-controlled study 1102.

21 Study 1102 is a 10-milligram, 20-milligram,  
22 and placebo-controlled study in osteoarthritis for

1 14 days. The FDA conclusion, quotes, "This  
2 double-blind, parallel group, dose-response study  
3 provides substantial evidence of the short-term  
4 analgesic efficacy of controlled-release oxycodone  
5 20 milligram in patients with this chronic pain  
6 model."

7 Also in Dr. Wright's review, he states,  
8 quote, "Oxycodone 20 milligrams separated from  
9 placebo within a week with an effect size of about  
10 0.4 or 0.6 or two-thirds SD." The 10 milligram was  
11 not effective -- not effective -- but provided  
12 information as a half-dose control. This data is  
13 not adequate by itself to support an OA indication,  
14 but is a very helpful trial in a non-oncologic  
15 chronic pain model.

16 This is the single adequate and  
17 well-controlled trial, study, identified by the FDA  
18 to approve OxyContin. This is an osteoarthritis  
19 study that the FDA stated is not adequate by itself  
20 to support an OA indication.

21 Let me say this again. One of the 2 doses  
22 used, the 10 milligram, was not effective, and the

1 20-milligram dose provided substantial evidence of  
2 the short-term analgesic efficacy. The  
3 40-milligram dose was not studied. The FDA knew  
4 OxyContin should not be approved, but they approved  
5 OxyContin 10 milligram, 20 milligram, and 40  
6 milligram.

7 Let me show you how I know the FDA knew the  
8 approval of OxyContin was wrong; wrong. By 2000,  
9 the FDA reported on OxyContin abuse in the opioid  
10 epidemic. These are FDA slides. The FDA knew that  
11 OxyContin should not have been approved, and the  
12 FDA was at a crossroads. Revoke the approval of  
13 OxyContin or cover up the approval.

14 This slide is the FDA minutes from a July  
15 14, 2001 meeting between the FDA, this division,  
16 and Purdue. Dr. McCormick is the director of this  
17 division. Let me quote and read the minutes.  
18 Dr. McCormick stated that the  
19 labeling -- started -- "began the labeling  
20 discussion by expressing the agency's concern about  
21 the clinical trials section. The trials currently  
22 in the label are pain models in artificial settings

1 with regard to the appropriate use of the product.  
2 The agency's position is that neither the  
3 osteoarthritis --" that's the 1102 study used to  
4 approve this drug -- "nor the single-dose  
5 postoperative pain study provide adequate data for  
6 a claim in the label."

7 How can you approve a drug if you don't have  
8 adequate data for the label?

9 "The studies as they were performed and  
10 described in the label are in contradiction to the  
11 indications we have inserted in the label. The  
12 sponsor believes that since the studies are  
13 placebo-controlled, they should be allowed to be  
14 remaining. Dr. McCormick stated that the studies  
15 must show separation of the study drug from placebo  
16 in the intended population and that the studies,  
17 which enroll patients based solely on their disease  
18 state rather than their pain status, and their use  
19 of, and the failure of other non-opioid  
20 medications, send a misleading message regarding  
21 the appropriate use of this drug."

22 Surprised we have an epidemic? There is no

1 question that OxyContin should have been revoked in  
2 2001. OxyContin should have been revoked in 2001.  
3 Instead of revoking OxyContin, FDA decided. without  
4 any additional clinical data, not one additional  
5 data submission, to change the label. They  
6 restricted the clinical trial section to the single  
7 adequate and well-controlled trial 1102.

8 Remember that when you vote today.

9 Remember, this is trial 1102, a 14-day trial in  
10 osteoarthritis, comparing 10, 20 milligram, and  
11 placebo. Again, in the FDA's own words, "The  
12 10 milligram failed. The 20 milligram provided  
13 substantial evidence of the short-term analgesic  
14 effect. And the 40 milligram was not studied. The  
15 OA study is not adequate to support an OA  
16 indication."

17 On this single efficacy study, the FDA has  
18 proceeded to approve 10, 15, 20, 30, 40, 60, 80,  
19 and at one time 160-milligram tablets of OxyContin.  
20 This is illegal, and somebody needs to be held  
21 accountable. The FDA's response to the opioid  
22 epidemic was to change the indication to management

1 of moderate to severe pain when a continuous,  
2 around-the-clock analgesic is needed for an  
3 extended period of time. There is no clinical  
4 evidence to support that indication or the approval  
5 of OxyContin.

6 The opioid epidemic begins in 1995 with the  
7 FDA approval of OxyContin, and you have a decision  
8 today. You can become the clean-up committee or  
9 continue to be the cover-up committee. Thank you.

10 DR. McCANN: Would speaker number 3 step up  
11 to the podium and introduce yourself? Please state  
12 your name and any organization you are representing  
13 for the record.

14 DR. KOLODNY: My name is Dr. Andrew Kolodny.  
15 I'm the co-director of the Opioid Policy Research  
16 Collaborative at Brandeis University, and I'm the  
17 director of Physicians for Responsible Opioid  
18 Prescribing. I have no financial relationships to  
19 disclose.

20 There's been a fair amount of discussion  
21 today about abuse-deterrent formulations. I'd like  
22 to call your attention to what I believe is a more

1 important issue, and it's an item you'll be voting  
2 on at the end of the day, which is the efficacy of  
3 REMOXY. It's not just my opinion that this is an  
4 important topic that you should be asking  
5 yourselves, have I been presented with substantial  
6 evidence of efficacy for the intended population;  
7 it's not my opinion that this is something you  
8 really need to seriously consider. It's the law.  
9 It's what the law says, the law on adequate and  
10 well-controlled studies for new drug applications.

11           And it says, quote, "Adequate and  
12 well-controlled investigations provide the primary  
13 basis for determining if there is substantial  
14 evidence to support the claims of effectiveness."  
15 So what information have you been presented with to  
16 make that determination?

17           I'd like to point your attention to page 58  
18 of the briefing document that you received, and I'd  
19 like you to look at the area that's highlighted.  
20 What you'll see is the highlighted sentence is  
21 referring to safety and efficacy on the basis of  
22 bioequivalence to Roxicodone. FDA is suggesting

1 that based on bioequivalence to Roxicodone, there's  
2 reason to believe that there's safety and efficacy.

3 That's a strange sentence because, by  
4 definition, an extended-release opioid is not  
5 bioequivalent to an immediate-release opioid. But  
6 putting the bioequivalence question aside, I think  
7 this would sort of make you wonder what happened in  
8 the Roxicodone NDA, what was the study that was  
9 done to demonstrate efficacy of Roxicodone.

10 So if you look at the Roxicodone new drug  
11 application and the medical review for it, what you  
12 would find out is that Roxane Laboratories was not  
13 required to produce an efficacy trial. Roxane  
14 Laboratories was given permission to bridge to  
15 Percodan, which is a combination product with two  
16 active ingredients that was on the market before  
17 FDA required efficacy studies. So there was no  
18 efficacy trial done for Roxicodone.

19 This is the next sentence in the briefing  
20 document. It refers to just one study that was  
21 done to provide information about efficacy. This  
22 is the Lynn Webster study. This is a poster for

1 that study, and this study was presented to you  
2 earlier today. I want to draw your  
3 attention -- this is a chart in that study. And  
4 I'd like to just describe this study in a little  
5 bit of detail.

6 The study enrolled 558 patients with  
7 moderate to severe osteoarthritis of the hip or  
8 knee. That is not the intended population for this  
9 drug. The label for this drug, the intended  
10 population, is quote, "Pain severe enough to  
11 require daily, around-the-clock, long-term opioid  
12 treatment for which alternative treatment options  
13 are inadequate."

14 That's not who the drug was studied, and  
15 showing that a drug is efficacious for patients  
16 with moderate to severe osteoarthritis pain is not  
17 the same as showing it's efficacious for patients  
18 with severe pain who have failed all other options.  
19 But it really gets worse if you look at the  
20 methodology that was used in this study. Some  
21 people call it enriched enrollment, randomized  
22 withdrawal. I think a better term for this type of

1 methodology is cooking the books.

2           The patients enrolled began by taking REMOXY  
3 titrated to 20 milligrams BID. That's equal to 60  
4 milligrams morphine per day, and they took that for  
5 2 weeks. By the end of the 2 weeks, 146 patients  
6 who didn't tolerate REMOXY, or didn't get adequate  
7 pain relief, or violated protocols were removed.  
8 That left 412 patients, the enriched sample. It  
9 was those 412 patients that were then randomized to  
10 either stay on REMOXY and be titrated up or to be  
11 switched over to placebo.

12           Anybody with clinical experience prescribing  
13 opioids would recognize immediately that there's a  
14 real problem here because if you take patients who  
15 are on 60 milligrams of morphine a day, and over  
16 2 weeks taper them down to placebo, the patients  
17 will experience worsening pain. Complaints of  
18 pain, pain hypersensitivity, and patients being  
19 withdrawn from opioids is extremely common.

20           Tapering people over 2 weeks is rapid. The  
21 clinical recommendations from CDC and other  
22 organizations are to taper patients by 10 percent

1 each week. Some recommend 10 percent a month.  
2 These are patients who should have been tapered off  
3 of 60 MME over several weeks or several months, not  
4 over 2 weeks. One would expect that these patients  
5 would have significant pain.

6 It's very difficult to describe this as a  
7 double-blind trial because the patients who were  
8 switched over to placebo after taking a strong  
9 opioid for 2 weeks to be given the sugar pill, the  
10 patients would probably know it, any of them. And  
11 these study clinicians would probably know it  
12 because those patients would be experiencing  
13 withdrawal symptoms. So this was also not a true  
14 double-blind study.

15 So in summary, the NDA for REMOXY does not  
16 include an efficacy trial in the intended  
17 population, not one. The only efficacy trial  
18 included in the NDA was performed on patients who  
19 are not the intended population, moderate to severe  
20 osteoarthritis pain. The only efficacy trial  
21 included in the NDA was not adequate and well  
22 controlled, which is required by the law.

1           If this is something that sounds strange to  
2 you, that FDA would move in this direction, you're  
3 in good company. At the request of Commissioner  
4 Califf, the previous FDA Commissioner, the National  
5 Academy of Sciences issued a report where they  
6 urged FDA to overhaul its opioid policies,  
7 particularly the way that it's approving new  
8 opioids.

9           Commissioner Gottlieb immediately endorsed  
10 the report. A year later, though, we've seen very  
11 little action, which has led to frustration,  
12 particularly among the National Academy of  
13 Science's panel members who have written a letter  
14 to the docket available to you to read, expressing  
15 concern about approval of opioids for chronic pain  
16 when we lack evidence of benefit, yet have  
17 significant evidence of harm.

18           A federal review has found the same.  
19 Fortunately, Purdue Pharma announced in February  
20 that it would cease promoting OxyContin for chronic  
21 pain. This is good news because despite recent  
22 declines in oxycodone prescribing, we are still

1       massively overprescribing. This is how we compare  
2       to oxycodone prescribing in Europe. The United  
3       States is blue. Europe is red.

4               Here's what the picture looks like today.  
5       You can see this is all opioids, and you see the  
6       prescribing really took off -- [microphone turned  
7       off].

8               DR. McCANN: Would speaker number 4 please  
9       come to the podium?

10              MS. HOLTUM: name is Lexi Reed Holtum. I am  
11       the executive director of the Steve Rummler Hope  
12       Network. I'm sharing my time today with Michael  
13       Daub, and I don't have any financial disclosures.  
14       I have 4 minutes to tell you the kind of  
15       destruction that this kind of pill does on the  
16       market, and I can't imagine -- and let me say thank  
17       you to all of you for giving me the time today.  
18       And I can't imagine that all of you who don't know  
19       someone that this has impacted the way in which our  
20       country has had its prescribing practices for  
21       opioids for the last 20 years. So I'm going to try  
22       and be really succinct, but I'm telling you, it's

1 impossible for me to tell you the story of Steve  
2 Rummler in 3 minutes.

3 Steve suffered an injury to his back in  
4 1996, and in 2005, he was prescribed time-released  
5 opioids. That started his journey into hell. He  
6 literally lost his life because he was prescribed  
7 opioids. In the beginning, he felt like it was a  
8 lifeline because somebody believed him that he was  
9 suffering with chronic pain, and they treated him.  
10 Very quickly after that, he became addicted. And  
11 in 2011, rather than planning our wedding, I ended  
12 up planning his funeral.

13 The namesake of our foundation is not alone  
14 in the journey that he walked. He was prescribed  
15 opioids to treat his pain. His doctor was taught  
16 that that was the right thing to do, and it killed  
17 him. And he like hundreds of thousands of  
18 Americans -- you know, as I listen today to the  
19 things that are being said, and I listen to the  
20 questions that you really intelligent people asked,  
21 one of the things that I walk away with is that the  
22 question could not be answered, what happened to

1 those patients that were in the study? What  
2 happened to those individuals afterwards? Did  
3 anyone follow up to see were they seeking opioids  
4 in some other form or fashion? Because that's  
5 what's happening across our country, is people are  
6 being prescribed into addiction, and 4 out of 5  
7 individuals that overdose and die from heroin  
8 started with prescription pain pills.

9 I beg of you, please do not -- do not  
10 approve any more opioids to market. We are working  
11 hard to clean up the problems that impact every  
12 social economic class in our country today, not  
13 just the individual, but the people that are left  
14 behind. We cannot afford to have another opioid go  
15 to market that has not been adequately,  
16 scientifically tested and proven that the benefits  
17 outweigh the risks.

18 I thank you for your time today. I'm happy  
19 to answer any other questions. And I just really  
20 appreciate the time to share. And please, we have  
21 to stop doing harm before we can create solutions.  
22 We are in a country that has a shorter life

1       expectancy because of our prescribing practices.  
2       And it is literally the definition of insanity to  
3       keep doing it the same way and expect different  
4       results. Thank you.

5               DR. DAUB: Good afternoon. My name is  
6       Michael Daub. I'm on the board of directors of the  
7       Steve Rummeler Hope Network, founded in the  
8       aftermath of the death of our namesake in 2011.  
9       We're from Minnesota. Our efforts led to the  
10      passage of what's called Steve's Law, which gave  
11      first responders the ability to carry naloxone on  
12      emergency calls and protect individuals who call  
13      911 from criminal prosecution. We're advocates of  
14      legislation to hold big pharma accountable. We  
15      provide overdose training throughout the state of  
16      Minnesota and offer prescriber education to the  
17      medical profession.

18             Almost 20 years ago, I became involved in a  
19      community of people who had recovered from  
20      substance-use disorders. I began mentoring men and  
21      women seeking to recover. I began volunteering at  
22      facilities, treating these people, and began trying

1 to help them overcome substance-use disorders. All  
2 of my efforts have been on a voluntary altruistic  
3 basis. I have no financial stake in any of this  
4 business.

5 I've been on the front lines. We call it  
6 being close to the flame. I need your help on your  
7 end. I believe I speak here today for people all  
8 across America who are lost, who feel that the deck  
9 is stacked against them. I also believe I speak  
10 for all of those who have suffered and are  
11 continuing to suffer. We've experienced an  
12 outpouring of support from our community simply  
13 because they know we're here today to speak up and  
14 to carry this message.

15 When I was a kid, I remember being in a  
16 grocery store. Over the loud speaker, the manager  
17 announced, "Clean up in aisle 3. Bring them up."  
18 The drug companies have made billions of dollars.  
19 They've made slick presentations. We're the people  
20 that are cleaning up the mess, and they fight us  
21 every step of the way. We tried to get some  
22 legislation passed this year, and they hired teams

1 of lobbyists to oppose our legislative efforts.  
2 They make enormous contributions to political  
3 campaigns. They pay tribute to lawyers by the  
4 truckloads to defend lawsuits brought by the  
5 hundreds, by governmental entities trying to  
6 recover monies that it's cost the taxpayers, again,  
7 to clean up the mess they created. It's a  
8 juggernaut. They need to be stopped. Someone,  
9 something needs to stand in the way.

10 The opioid epidemic is engulfing the United  
11 States. I've watched with great pleasure recovery  
12 successes, but I've observed far too many people  
13 fail, succumbing to addiction again and again.  
14 Barely a week goes by where I don't get a call that  
15 someone's died of an overdose, sometimes two,  
16 sometimes three.

17 I had a discussion the other day with a  
18 OB-GYN doctor about neonates, and how the neonates  
19 end up in ICU. These are our sons. These are our  
20 daughters. These are our friends. These our  
21 neighbors. These are our co-workers, good people  
22 failed by a pernicious, unforgiving, relentless

1 malady. It annihilates all things worthwhile in  
2 life. It engulfs all whose lives touched the  
3 sufferers. It brings misunderstanding, fierce  
4 resentment, financial insecurity, disgusted friends  
5 and employers, more lives of blameless children.  
6 Children without parents is a big issue the last  
7 few weeks. We can tell you all about children  
8 whose parents have died.

9           Americans everywhere are affected.  
10 Communities are overrun by despair. Suicide is  
11 more prevalent than ever before. I've read the  
12 National Academy of Science's report, which is  
13 quoted in one of the letters that you've received.  
14 Years ago, I remember watching the movie, Thank You  
15 for Smoking, and they called the lobbyists the  
16 merchants of death.

17           Well, why do I feel that life is imitating  
18 art? These people are pariahs. They've pulled the  
19 wool over your eyes time and time and again.  
20 They're a bunch of liars, thieves, and scoundrels  
21 dressed up in business suits. They've stolen the  
22 soul and dignity of billions of millions of

1 Americans. They've decimated family values.  
2 They've robbed the economy of billions of dollars  
3 of productivity. They have cost counties, cities,  
4 and states billions of dollars. Trying to regulate  
5 them and do business with them is like trying to  
6 herd cats. Please forgive me. I'm a cat lover.  
7 They shake your hand, and at the same time, the  
8 knife you in the back. They've been fined millions  
9 of dollars, but they keep moving forward.

10 I've read a little bit lately about this  
11 constitutional claim that they can disseminate  
12 health claims about their product without first  
13 submitting their claims to the FDA. They are  
14 challenging your authority is how I look at it.  
15 That's how far they've pushed the FDA and the  
16 American people, and thousands of people have died  
17 as a result. I can't believe we're sitting here  
18 having a conversation where there's been collateral  
19 damage that's cost 200,000 or more lives. We went  
20 to war because 3,000 people died back on 9-11. So  
21 what are we going to do about 200,000 people? Is  
22 that just a drop in the bucket?

1           I can't talk on the level of the experts.  
2           I'm not a doctor. I can't deal with it from a  
3           technical level. But I have this other memory as a  
4           kid. What did they teach us in the third grade?  
5           In 1937, Congress passed the Food, Drug, and  
6           Cosmetic Act in response to the death of 107 people  
7           who died from an ingestion of an adulterated  
8           elixir. The defining moment of the FDA occurred in  
9           the case of thalidomide, thanks to the  
10          perceptiveness and determination of a single new  
11          reviewer at the FDA, Dr. Frances Kelly [sic -  
12          Kelsey]. The drug was denied approval.

13                 So I ask you this. Thalidomide was kept off  
14          the market, and American people were protected.  
15          What would Dr. Kelly [sic] do today? Thank you.

16                 DR. McCANN: Will speaker number 5 step up  
17          to the podium and introduce yourself? Please state  
18          your name and any organization you are representing  
19          for the record.

20                 DR. WOLFE: I'm Sid Wolfe, Public Citizen  
21          health research group. I have no financial  
22          conflict of interest. I will briefly go over the

1 first couple of slides because the points have been  
2 made by the FDA previously. The first, the main  
3 point is that between 2010 and 2015, there were a  
4 total of 32,000-plus deaths associated with  
5 oxycodone, and the number per year really stayed  
6 the same. And this was stated by FDA correctly as  
7 a reason to think about as we consider another  
8 opioid being approved, whether there may be some  
9 net harm as opposed to any net benefit.

10 The next slide, again from the epidemiology  
11 presentation, simply pointing out, and I think  
12 everyone knows, that oral abuse is the most common  
13 form of abuse leading to treatment, deaths, and so  
14 forth. And within that, ER/LA oxycodone makes up  
15 about a good chunk of these, and 60 percent are  
16 with abuse-deterrent properties, so-called -- and  
17 again, the FDA has said there has never been a  
18 study submitted, really, based on good  
19 epidemiologic evidence showing that abuse  
20 deterrence works.

21 This to me was the most striking slide or  
22 piece of information in the whole briefing package

1 back last Friday, and it really shows the bottom  
2 line is intact REMOXY, and the middle Line is  
3 chewed REMOXY. And I can't think of any easier way  
4 of misusing or abusing -- as it may turn out to be,  
5 starting out with misuse -- and turning an ER,  
6 long-acting product into an instant one.

7           Essentially what happens here is that it  
8 takes 4 or some hours for the intact one to reach  
9 its maximum, whereas the chewed one is less than a  
10 half an hour, maybe 20, 25 minutes. I didn't do  
11 the exact calculations. So the slope, the rapidity  
12 of increased blood concentrations and relief from  
13 pain and so forth, is infinitely higher with the  
14 chewed version. Chewing something is not a big  
15 deal. You extract it with your mouth. There was a  
16 question asks about transmucosal absorption. I'm  
17 sure that once you chew it, some of it gets in that  
18 way; some of it gets in through the stomach.

19           The next slide is just a little more detail  
20 on this, and I would like to focus on the bottom  
21 line, the area under the curve. And what you can  
22 see is that translated into English at an hour is

1 about 8 times more chewed REMOXY getting into the  
2 body than the unchewed. And because the last slide  
3 is linear, this actually starts out right at the  
4 beginning. So with even 10, 20, 30 minutes, you  
5 already are getting much more, about 8 times more,  
6 into your body with the chewed one than with the  
7 intact one.

8           These are just briefly some of the findings  
9 from the oral abuse study, particularly before  
10 501-016. I mentioned before that the maximum  
11 concentration for REMOXY, unchewed and so forth, is  
12 at 4 hours -- it occurs at 30 minutes with the  
13 chewed version. And then in another study, there's  
14 a threefold increase in the concentration of REMOXY  
15 when it was chewed as opposed to not being chewed.

16           This one is simply talking about -- it's  
17 middle bar -- chewed REMOXY 40 has a statistically  
18 significantly larger -- meaning Emax, and these are  
19 liking measures -- than intact REMOXY. And the  
20 FDA's conclusion, stated I think mildly, in the  
21 briefing package was, "The earlier Tmax," time of  
22 maximum concentration, "and the high relative of

1 bioavailability compared with the intact indicate  
2 that the proposed product may not deter oral abuse  
3 by chewing."

4 This is the question, and this is not asked  
5 in this kind of way at all in the briefing package.  
6 But the question is, does the United States need  
7 another oxycodone product? Dr. Hertz correctly  
8 said that if a product, whether it is the 4th or  
9 5th or 10th, meets the FDA criteria, having one  
10 more needs to be  
11 acceptable, I suppose. But these are data from the  
12 most recent report from the U.N. International  
13 Narcotics Control Board, the narcotics drug report.  
14 It comes out annually. It came out about six or  
15 seven months ago.

16 "Consumption of oxycodone was concentrated  
17 in the United States where 72.9 percent of the  
18 world total was. Global consumption was 79.6 tons,  
19 meaning 58 tons of oxycodone were consumed in the  
20 United States that year." How much is this? And I  
21 just did some sort of simple calculations.

22 Fifty-eight tons is 58,000 metric tons or

1 58,000 kilograms, which is 58 billion milligrams.  
2 And since the accepted dose, which is about 2 of  
3 the extended-release REMOXYS, is 75 milligrams,  
4 according to the U.N.'s calculations, this means  
5 that there are 773 million daily doses of oxycodone  
6 in the United States, which is by far the world  
7 leader in oxycodone consumption. In fact, it's the  
8 world leader in total opioid consumptions also.

9 If you look at all of the other countries,  
10 all but 6 of the 166 other countries that are  
11 measured by the U.N. have less than one-quarter the  
12 amount of population adjusted opioid as the United  
13 States does.

14 So on to the discussion questions, oral  
15 route of administration. And the question is, has  
16 it been expected to deter abuse? It will likely  
17 increase this predominant form of abuse, increase,  
18 and misuse also -- because you might say that when  
19 a doctor gives out a prescription for this drug,  
20 and says please don't chew it because if you do,  
21 more will be released, you'll get sooner relief  
22 from your pain and so forth. I mean, this kind of

1 conversation is really unacceptable, which is why  
2 this drug I think is unacceptable.

3 So the answer is it will not deter abuse.  
4 It will likely increase misuse and abuse, and thus  
5 it's abuse or misuse enhancing, not deterring. I  
6 had not seen, until today, the FDA's look at the IV  
7 abuse and pointing out that it really cannot be  
8 said to be IV resistant, IV abuse resistant.

9 Finally, the last question is, do we have  
10 concerns regarding the impact on the public health?  
11 Yes. For reasons stated by the FDA and discussed  
12 today, impact on increased oral abuse is very  
13 likely if not certain. And finally, should it be  
14 approved? No. Since neither your committees, nor  
15 the FDA, want to further increase U.S. oxycodone  
16 abuse, a likely if not certain outcome of REMOXY is  
17 approved.

18 The idea that there are no alternative --  
19 [microphone turned off].

20 **Clarifying Questions (continued)**

21 DR. McCANN: Thank you. That concludes the  
22 open public hearing portion of this meeting, and we

1 will no longer take comments from the audience.  
2 What we'd like to do right now is finish up with  
3 the comments for the questions for the sponsors,  
4 and I believe we have at least four questions. So  
5 we'll start off with Dr. Zeltzer.

6 DR. ZELTZER: This question, I'm not sure  
7 whether it's for Pain Therapeutics or really for  
8 you, Sharon. If we think about unintended  
9 consequences, we can almost assume that even though  
10 there is not an indication should this get FDA  
11 approval for use in children, adolescents will  
12 likely access and use the drug, misuse the drug,  
13 abuse the drug.

14 I guess in terms of even safety -- I mean,  
15 let alone all the other issues, but safety  
16 data -- given that the studies were done in  
17 adults -- and I guess the closest -- while  
18 pharmacodynamics and pharmacokinetics are different  
19 in children than in adults -- they're not just  
20 little adults -- the closest thing you would have,  
21 at least in the HIV population tested, are smaller  
22 body weights, at least for some of the population.

1           Was there any data looking at body mass  
2 index in outcomes just in terms of the basic safety  
3 of the product, let alone all of the other  
4 parameters? Again, I'm thinking of more basic  
5 safety questions given that if this is given -- if  
6 this is out on the market and given FDA approval  
7 for the indications requested, it will be used by  
8 adolescents, who are different.

9           So I don't know. -- they're really probably  
10 several questions within that.

11           DR. HERTZ: This is Sharon Hertz. I'm not  
12 quite sure what the final question is.

13           DR. ZELTZER: So the final question for Pain  
14 Therapeutics is, are there, I guess, adverse events  
15 and SAE data, just to get to this point, in  
16 smaller, significantly less than 50-kilogram  
17 adults, given that you only looked at adults? And  
18 using the HIV population, there might be at least  
19 enough of a subcohort that might be more pediatric  
20 size even though there are a whole lot of  
21 differences; so just as a basic risk factor, let  
22 alone the risks of the different components that

1 are in there.

2 So that's probably one question, and then  
3 maybe address that, and then, Sharon, I can ask the  
4 FDA question.

5 DR. FRIEDMANN: This product is not intended  
6 for children. We collected BMI data, but we have  
7 not analyzed to look at outcome versus BMI data.  
8 We probably can discuss it with the FDA if they  
9 need it.

10 DR. ZELTZER: So, Sharon, the broader  
11 question?

12 DR. HERTZ: Every NDA is required to have a  
13 pediatric plan, a pediatric study plan, by the  
14 time -- well, certainly by the time they file an  
15 NDA, and there are other time criteria within  
16 there. Deciding which products should be studied  
17 in children and when to study them is always  
18 challenging, particularly when it comes to an  
19 opioid.

20 To that end, we've had some discussion of  
21 this at two advisory committee meetings. We  
22 introduced the concept at a meeting of the

1 Pediatric Advisory Committee and followed that up  
2 with an advisory committee meeting specifically  
3 dedicated to the evaluation of opioid analgesics in  
4 children.

5 Children need pain management as much as  
6 other age groups. Early-life exposure to pain can  
7 have long-term effects. Children have needs for  
8 analgesics that are different than adults,  
9 particularly when it comes to chronic pain  
10 conditions. So yes, opioids need to be available,  
11 but as mention, we also heard during that same  
12 advisory committee -- it was a very elegant talk by  
13 a clinician whose name I cannot bring to mind  
14 immediately, but who described the effects of  
15 exposure of the adolescent brain to substances that  
16 may have abuse potential, opioids included. And  
17 that creates a variety of risks and potential  
18 downstream problems.

19 So then the question is, when should an  
20 adolescent even be treated with an opioid? And the  
21 answer may be much more infrequently than currently  
22 occurs. So when to study an opioid in a child,

1 it's challenging. With the abuse-deterrent  
2 opioids, some of the limitations are based on  
3 formulation and being able to achieve dosages that  
4 are appropriate for smaller bodies, for  
5 weight-based dosing. A number of them have failed.  
6 Also, is there a chronic pain population for whom  
7 they're even appropriate?

8           So have I kind of covered the issue? I'm  
9 sort of skirting whether or not this product should  
10 specifically be studied. There are a series of  
11 questions that have to be answered by the applicant  
12 with regard meeting their requirements for  
13 pediatric studies that everybody has. We take all  
14 of those pediatric study plans to the pediatric  
15 research committee and discuss them there.

16           I can tell you that we have been constantly  
17 monitoring the outcome of one of the more recent  
18 pediatric approvals for OxyContin. That data so  
19 far have actually shown that in contrast to  
20 concerns expressed, prescribing of OxyContin has  
21 decreased in children not increased. That might  
22 be, in part, because of a number of factors

1 completely unrelated to the action, as well as  
2 narrowing the indication for pediatric patients for  
3 that drug beyond what had already been the standard  
4 of practice.

5 So that's what I have to say.

6 DR. ZELTZER: Thank you. I just felt like  
7 we needed to have that piece of it discussed.  
8 Thanks.

9 DR. McCANN: Ms. Robotti?

10 MS. ROBOTTI: Hi. Suzanne Robotti. A  
11 question for Pain Therapeutics. I'm not sure to  
12 whom directly to address. What was the effect on  
13 fertility that you found in your study? You had a  
14 study on fertility.

15 DR. FRIEDMANN: In animals.

16 MS. ROBOTTI: Sure. What was the effect?

17 DR. MONTGOMERY: Well, there hasn't been any  
18 [inaudible - off mic.]

19 DR. McCANN: Use the microphone, please.

20 DR. MONTGOMERY: As far as we know, there's  
21 been no effects on fertility or reproduction for  
22 these excipients, because that's all we're really

1 talking about.

2 MS. ROBOTTI: For the excipients, not for  
3 the opioid itself.

4 DR. MONTGOMERY: No. We haven't done any  
5 studies ourselves on the opioid.

6 MS. ROBOTTI: You didn't study that at all?

7 DR. MONTGOMERY: No.

8 MS. ROBOTTI: And did you bring your  
9 pregnancy and lactation label? Can you show us  
10 that?

11 DR. MONTGOMERY: I'm sorry?

12 MS. ROBOTTI: The pregnancy and lactation  
13 label, did you bring that? Can we see that?

14 DR. MONTGOMERY: No.

15 DR. HERTZ: This is Sharon Hertz. I'm going  
16 to introduce Dr. Dan Mellon. He's our supervisory  
17 pharmacologist/toxicologist and has done a fair  
18 amount of work in this area, and has also  
19 supervised the review of this application in the  
20 nonclinical work.

21 Dan, can you just give an overview of the  
22 nonclinical data, and in particular some of the

1 data regarding repro-tox?

2 DR. MELLON: Sure. Again, this is Dan  
3 Mellon, a pharm-tox supervisor in DAAAP. This  
4 program is relying upon an agency previous finding  
5 for another product. And as a result from the  
6 opioid perspective, the product will be labeled  
7 identically to the product that is currently  
8 marketed.

9 In that program, they had what's referred to  
10 as segment 1 and segment 2 studies that were  
11 completed in rats and rabbits. The studies are  
12 designed to try to understand the impact of the  
13 opioid during organogenesis. There were also, if  
14 I'm not mistaken, some fertility studies that were  
15 done.

16 The effects are pretty much what you see for  
17 most opioids. There is always a little bit of a  
18 signal on some fertility endpoints with opioids at  
19 higher doses in animals. The translation of that  
20 into the clinical setting is still a very complex  
21 issue and is not entirely clear. But the product  
22 will be labeled identically to the reference

1 product with respect to that.

2 The primary tox program here that was put  
3 together was with respect to several novel  
4 excipients that were being utilized for this  
5 particular formulation. And when we reviewed the  
6 overall tox program for this, we felt that we had  
7 all of the information that was necessary to  
8 appropriately evaluate the safety of the  
9 excipients.

10 And just for your own edification, any time  
11 a new novel excipient is being utilized and  
12 proposed for a drug product, they actually are  
13 required to do all of the exact same studies that  
14 you would do with a new molecular entity. So we  
15 evaluated that program, and we believe that we have  
16 adequate safety margins for the intended route, and  
17 even for an opioid-tolerant individual.

18 MS. ROBOTTI: Just to follow up, so a  
19 pregnant woman would be able to get clear direction  
20 from her doctor, obstetrician; or a woman who's  
21 planning on being pregnant, she could get clear  
22 direction from her doctor about using an opioid.

1 There's information that's useful and appropriate.

2 DR. HERTZ: There is information that  
3 describes the nonclinical findings. There is some  
4 information that describes some of the clinical  
5 concerns. There are warnings about neonatal opioid  
6 withdrawal syndrome. Those are in the opioid  
7 labels. Whether or not a woman who is pregnant  
8 should be managed on opioids is a huge question;  
9 opioids for pain. Let's be very specific, because  
10 opioids for management of addiction is a very  
11 different risk-benefit.

12 So that discussion should take place in the  
13 context of what is the woman's situation with  
14 regard to pain, what other alternatives are  
15 available, and knowing that there will be some  
16 concerns about risk, how does that individual  
17 balance the risk with the concern for pain  
18 management.

19 MS. ROBOTTI: And my point would be that  
20 this is a large population, a recurring new  
21 population every year, that doesn't really have  
22 clear direction on it. And I mean when prescribed

1 and used appropriately. I'm not talking about an  
2 abuse or misuse situation. And I know that the  
3 directions in REMS says that the bar should be  
4 raised every higher; that simply because a REMS  
5 solution was appropriate five years doesn't mean  
6 that we shouldn't hold a new applicant to a higher  
7 standard.

8 So I would suggest that going forward, we  
9 should be getting information on all populations  
10 who use this drug: seniors, pregnant women, and  
11 anyone else is a subpopulation.

12 DR. McCANN: In the interest of time, we're  
13 just going to take the last three questions that  
14 were submitted before; not people who are coming up  
15 with new questions. I apologize, but I don't want  
16 people to miss their transportation home.

17 So we have Dr. Prisinzano, please.

18 DR. PRISINZANO: Tom Prisinzano, University  
19 of Kansas. I guess my question is for the sponsor,  
20 probably most appropriately, Dr. Crowley. So can  
21 you give me your perspective on the differences  
22 that we see between the studies that you presented

1 versus the studies that the FDA had approved in  
2 terms of the amount of compound that's extracted?

3 DR. CROWLEY: So the question is commentary  
4 on the differences between the work done at our  
5 third-party labs and what the FDA found in theirs.  
6 We have not had an opportunity to speak with the  
7 agency to see how they did do their studies. In  
8 looking at one of the tables, it was performed at a  
9 different temperature, a higher temperature, than  
10 the highest temperature that we did.

11 We stand by our data. It was performed at  
12 two different laboratories that have done category  
13 1 studies before. The FDA data is real data.  
14 There are going to be differences. I suspect that  
15 there were some differences between the way in  
16 which ours were done and the way in which the FDA  
17 did do theirs.

18 DR. PRISINZANO: Thank you.

19 DR. McCANN: Ms. Spotila?

20 MS. SPOTILA: Jennifer Spotila. It's a  
21 question for PTI. I just want to get some final  
22 clarification on phase 3 and the study cohort. You

1 were asked about age. I think you said over 40.  
2 You were asked about gender. You said male/female,  
3 but you didn't give us a breakdown.

4 What about co-morbid medical conditions and  
5 other medications, and especially in the subjects  
6 who were on the open-label trial for 6 and 12  
7 months? Can you give us a characterization of  
8 those?

9 DR. FRIEDMANN: Not offhand. All the  
10 information is NDA. Patients were on multiple  
11 drugs. There were no drug interactions. They are,  
12 I would guess, 50 to 100 different products that  
13 they were on. We did not see any issues.

14 MS. SPOTILA: And co-morbid medical  
15 conditions?

16 DR. FRIEDMANN: I don't recall issues.

17 DR. McCANN: Dr. Hertig?

18 DR. HERTIG: John Hertig, Purdue University.  
19 Just a practical scenario question. So say a  
20 patient is prescribed this. If approved, they have  
21 trouble or difficulty swallowing, so they good  
22 intentionally cut open or otherwise get into the

1 capsule, and then scrape out the inside and put  
2 that on applesauce or whatever modality. What do  
3 you expect in that situation that the patient would  
4 experience in terms of drug effect and any adverse  
5 outcome?

6 DR. FRIEDMANN: I do not expect an issue.  
7 As I mentioned earlier -- and you can put one of  
8 the slides -- the Cmax that you get with REMOXY  
9 chewed is the same Cmax that you're going to get  
10 with Xtampza intact. So from a safety point of  
11 view, I don't see an issue. Okay?

12 First of all, if they take it from the  
13 capsule, you're going to lose a lot of material.  
14 They won't be able to get a hundred percent of the  
15 capsule out, as Dr. Crowley said. You're probably  
16 going to lose 10 to 25 percent. Beyond that, we  
17 have not done the study, so I cannot tell you what  
18 to expect, but I don't believe there are going to  
19 be issues.

20 DR. HERTIG: Thank you.

21 DR. McCANN: So that concludes our questions  
22 to the sponsor. The committee will now turn its

1 attention to address the task at hand, the careful  
2 consideration of the data before the committee, as  
3 well as the public comments.

4 So Dr. Sharon Hertz will now provide us with  
5 a charge to the committee.

6 **Charge to the Committee - Sharon Hertz**

7 DR. HERTZ: Do opioid analgesics work? Do  
8 they work for chronic pain? Do enriched randomized  
9 withdrawal designs demonstrate efficacy? Yes, to  
10 all of them. We have data. We have data for all  
11 of them. We have clinical studies in which  
12 patients who have been managed on opioids for  
13 months and years go into a randomized withdrawal  
14 treatment study design, and then after 12 more  
15 weeks, we can show that compared to the group not  
16 on the active agent, there's efficacy.

17 They work. This whole debate about absence  
18 of evidence being evidence of absence has really  
19 gone entirely too far, and patients are currently  
20 being harmed as a result of a complete breakdown in  
21 scientific thinking and data application when it  
22 comes to this topic.

1           The question isn't do opioids work and can  
2 they treat chronic pain when we're talking about  
3 public health. Who is the intended population for  
4 opioids? That's one of the important questions for  
5 public health. Why do we have an opioid epidemic?  
6 Why do we in this country use 90 percent, or  
7 whatever the figure is, of the world's opioid  
8 analgesics? Why are so many prescribed in the  
9 U.S.? Why is there no opioid crisis in Europe?  
10 They have the exact same drugs approved. The same  
11 drugs are marketed. So do we want to blame the  
12 drugs? There's got to be something else.

13           Who's responsible for the opioid crisis?  
14 Sponsors? Distributors? Prescribers?  
15 Pharmacists? Patients? Who's responsible? I  
16 don't think there's one targets. Are we  
17 responsible? There's no one target.

18           Maybe the question we should be asking is,  
19 what is the appropriate management of chronic pain  
20 and how can we deliver that to patients? I don't  
21 think anybody in this room would argue that simply  
22 prescribing an opioid analgesic in the absence of a

1 comprehensive pain management treatment plan is  
2 appropriate, adequate management for chronic pain.

3 So what is appropriate management for  
4 chronic pain? Is it accessible to the patients who  
5 need it in this country? What is available to  
6 patients in this country?

7 There's an AHRQ technical brief from 2011.  
8 It's technical brief number 8, Multidisciplinary  
9 Pain Programs for Chronic Non-Cancer Pain. I  
10 recommend everybody read this. It's a very  
11 important and interesting review on the status of  
12 this evidence-based approach to managing chronic  
13 pain in the country as of 2011, and there's no  
14 reason to think it's gotten any better. And I'm  
15 going to give you a few quotes from this article,  
16 and then I'm going to get us back on track to the  
17 questions at hand.

18 These are quotes from the article. Some of  
19 them are re-quotes from sources, but I'm not going  
20 to identify all of these right now.

21 "The goal of chronic pain treatment has  
22 evolved from eliminating pain to managing pain to

1 an extent that patients' physical and emotional  
2 functioning is restored and overall quality of life  
3 improved. This is the model of care provided by  
4 the Multidisciplinary Pain Program. There is no  
5 single protocol for treatment in MPPs. There is  
6 general agreement on some included methods."

7 One of the findings of this report was that  
8 there's been a decline in the number of MPPs in the  
9 United States, and in parentheses, "the number in  
10 other countries may actually be growing." There  
11 are dichotomies that have been identified in this  
12 report from some of the contributing sources that  
13 have held the MPP back from being the recognized  
14 standard care in the United States; its  
15 disciplinary collaboration in MPPs versus  
16 discipline segmented organization of major medical  
17 centers; and collaborative care in MPPs versus the  
18 fee-for-service model of health care payments.

19 "Rehabilitative treatment in MPPs focused on  
20 individual assessment and patient behavior change  
21 versus the curative medical model of treatment. In  
22 each of these dichotomies, the MPP model runs

1 counter to the prevailing architecture of American  
2 healthcare, financing, and provision. According to  
3 the experts consulted, the treatments most likely  
4 to be carved out from MPP are physical therapy and  
5 psychological behavioral therapy."

6 This goes on for a very um, important and  
7 detailed discussion. And one final quote,  
8 "Paradoxically, the efficiency of carve outs,"  
9 referring to approaches to paying for pain  
10 management therapy -- "paradoxically produce the  
11 effect of steering patients away from  
12 multidisciplinary treatments that demonstrably  
13 reduce healthcare utilization toward more extensive  
14 unimodal therapies associated with poor outcomes."

15 So getting back to the subject of today's  
16 advisory committee and moving away from the  
17 question of whether this drug's approval or  
18 non-approval is a specific answer to the opioid  
19 crisis, you've heard the presentations from the  
20 company, from us, about clinical data and about  
21 these different assessments of abuse-deterrent  
22 properties. You've heard about some of the

1 differences in our findings based on lab work.

2           During the discussion of the questions,  
3 you're free to comment on anything that has come up  
4 during the meeting, any of the data provided as it  
5 influences your decision and your approach to  
6 answering the questions including anything that we  
7 may not have ever. So I say let's go on and get  
8 directly to the questions, and go from there.

9           **Questions to the Committee and Discussion**

10           DR. McCANN: Thank you. We will now proceed  
11 with the questions to the committee and panel  
12 discussions. I would like to remind public  
13 observers that while this meeting is open for  
14 public observation, public attendees may not  
15 participate except at the specific request of the  
16 panel.

17           So I'll read the first question. Please  
18 discuss whether the applicant has demonstrated that  
19 REMOXY extended-release, oxycodone extended-release  
20 capsules, has properties that can be expected to  
21 deter abuse, commenting on each of the following  
22 routes of abuse: A, oral; B, nasal; C,

1 intravenous.

2 If there are no questions or comments  
3 concerning the wording or the question, we will now  
4 open the question to discussion. Dr. Meisel?

5 DR. MEISEL: Steve Meisel with Fairview.  
6 Yes. I think one of the challenges for today, and  
7 frankly for all of the drugs that are in the  
8 pipeline and have been in the pipeline and that are  
9 in this class, is the definition of the phrase  
10 "expected to deter abuse."

11 I think it's been well stated at the  
12 beginning of today that abuse deterrence is not  
13 abuse. It's not 100 percent. It's not a black or  
14 white. And what does the term "deter" mean? Is it  
15 1 percent less likely to be abused than the  
16 reference product. And what is the reference  
17 product? Is the reference product OxyContin? I  
18 don't think that's always clear. Or is it the  
19 rapid-release products?

20 "Can be expected" is a term that is, in my  
21 view, softer than the term "proven to deter abuse."  
22 There's been evidence from the applicant that for

1 all three of these, that there is a reasonable  
2 expectation that compared to some of the reference  
3 products, it might be less likely to be abused. Is  
4 it hard evidence that it will be less likely to be  
5 abused, by what quantity? I have no idea. That  
6 hasn't been proven for this. It hasn't been proven  
7 for, to my knowledge, any of the products out  
8 there.

9 So it seems to me that if we say no to this  
10 and then deny this application, then it's incumbent  
11 upon the agency to go back and perhaps rethink its  
12 approach to this entire topic, because the guidance  
13 document that's been put together about abuse  
14 deterrence and so forth is really geared to  
15 encourage manufacturers to create products like we  
16 have seen today. And if we don't believe that  
17 that's enough, then maybe nothing is enough. And  
18 then maybe the whole concept of abuse deterrence is  
19 a concept that's inherently flawed, and we should  
20 move on to something else.

21 But in terms of this specific question, has  
22 it been expected to deter -- do the

1 properties -- are those properties that can be  
2 expected to deter abuse for oral, nasal, and  
3 intravenous? Yes, there is evidence for that.  
4 There's some contravening evidence that the agency  
5 has as well, but there is some reasonable evidence  
6 that it can deter abuse. Whether it will, I have  
7 no idea. And my guess is, if it does, it'd be very  
8 little.

9 DR. McCANN: Dr. Nelson?

10 DR. NELSON: Well, I would say that they've  
11 not demonstrated the ability to prevent abuse in  
12 any of these three realms, and I'll go through each  
13 one real quickly.

14 The oral data is the most clear because  
15 chewing the tablet or the pill produces blood  
16 levels that are close to that from the  
17 immediate-release formulation. And while they're  
18 lower than they would be from an intact pill,  
19 they're still substantially elevated, which to me  
20 means that it hasn't done anything to deter abuse.

21 What the blood level is that's required to  
22 make something abusable is unclear. But if you

1       assume that the intact pill is the ceiling, this  
2       one is substantially higher than that, and it's  
3       almost as high as the immediate release, which we  
4       think is abuse prone. So to me, oral is a  
5       non-starter. There's no evidence to show that.

6               The intranasal use I think is a little bit  
7       more questionably beneficial, but I don't think it  
8       actually supports a benefit because you can still  
9       get a substantial amount of drug out of the pill.  
10       And we see that by the blood levels in the  
11       patients -- or not the patients, but the subjects  
12       who were getting the medication administered to  
13       them intranasally. They were getting blood levels  
14       somewhere about 20 nanograms per milliliter, which  
15       is about the same level you get them a 10-milligram  
16       oral oxycodone tablet, immediate release.

17               So while it does reduce the amount of drug  
18       you can get into your body through that route, it's  
19       still very well absorbed and administered. And  
20       since there's no limit to the number of pills you  
21       can abuse, taking one pill gets you to 20; taking  
22       5 pills gets you a 100. It doesn't really seem

1       like it would deter abuse unless we limited the  
2       amount of pills anybody could have to 1, which  
3       we're not going to be able to do.

4                So I think while it might slow down the  
5       ability to abuse it, which is why I say that there  
6       might be some argument that there is some benefit  
7       relative to the levels that you'd otherwise get, I  
8       think it's pretty clear that it will not deter  
9       abuse because people can use more than a single  
10      pill.

11               The intravenous data I think is very  
12      confusing given the different findings of the two  
13      groups. I don't know what to make of it. I'm very  
14      concerned about -- as has been mentioned in several  
15      places -- the historical problems with injecting  
16      incipients [sic - excipients] that we don't  
17      understand. So while it might maybe deter abuse,  
18      the consequences might be much more far-reaching  
19      than even that.

20               So short answer to a long question or a long  
21      answer to a short question, I would say we've not  
22      seen any evidence for any of these.

1 DR. McCANN: Dr. Brent?

2 DR. BRENT: Thank you. Jeffrey Brent.  
3 There's a there's a narrow question and there's a  
4 broad question here, implicit within this  
5 discussion a question. And I'm not sure we're  
6 going to be able to address the broad one today,  
7 but I think it's one that we really need to take  
8 into consideration when we look at abuse-deterrent  
9 formulations.

10 Abuse-deterrent formulations is a great  
11 idea. They have lots of sort of intuitive benefit,  
12 and I know FDA feels strongly about them. But like  
13 every great idea, there can always be the  
14 unintended consequences. And certainly what we  
15 have learned from the OxyContin story is that  
16 abuse-deterrent formulations can accelerate  
17 transition to intravenous illicit opioids,  
18 specifically heroin.

19 There's very good data that a significant  
20 amount of this explosion that we are experiencing  
21 right now in heroin use and heroin contaminated  
22 with synthetics like fentanyl and fentanyl

1 derivatives, really derives directly from OxyContin  
2 becoming a so-called abuse deterrent formulation,  
3 so people could no longer use it intravenously and  
4 then had to turn to these other routes.

5           So there is this sort of broad issue about  
6 the wisdom of moving forward with yet another  
7 abuse-deterrent formulation, realizing that while  
8 it might be a good idea, it is also likely to  
9 contribute to the growth of intravenous heroin  
10 abuse.

11           In terms of the more narrow question of the  
12 demonstration of the abuse deterrence of this  
13 particular preparation, I'd have to agree with  
14 Dr. Nelson that it's probably not very abuse  
15 deterrent via the oral route. And I realize  
16 they're not asking for a label, that as it is, so  
17 that's not a concern. And there may be some abuse  
18 deterrent from nasal use, and we're not really  
19 going to concern ourselves with smoking. And then,  
20 of course, we do have the problem of the  
21 insufficiently characterized excipients that may  
22 play a role in intravenous use.

1           So I do have some concerns about approval  
2 with regard to these considerations.

3           DR. McCANN: Thank you. Dr. Brown I believe  
4 is on the line.

5           DR. BROWN: Thanks, Mary Ellen. I have some  
6 significant concerns. and I in general agree  
7 completely with the last two speakers. And I  
8 disagree with much that has been said. The  
9 problems that we come up against as we evaluate  
10 these ADFs, and have evaluated them in the past,  
11 has been that prescribing is very easy, and  
12 comprehensive care is not very easy, and it's  
13 expensive.

14           Why are we worse than the people in Europe?  
15 Well, opioids are marketed much more aggressively  
16 in the United States than in Europe. There's a  
17 problem with the method that we have used to  
18 suggest that oxycodone is efficacious, and that's  
19 been demonstrated today.

20           So the issue that we can't answer, that  
21 Dr. Hertz suggested was a non-starter, is whether  
22 or not chronic administration of opioids is a

1 reasonable thing to do in a broad population of  
2 patients. It could be and is a reasonable thing to  
3 do in very carefully selected patients, but we have  
4 to be judged against protecting the entire  
5 population, and that is one of the problems that we  
6 see as we try to understand these drugs.

7 We've been down this road before. We know  
8 from the last 10 ADFs that we've evaluated that  
9 they can all be manipulated. In many cases they  
10 are being manipulated while we're having advisory  
11 committee meetings. The importance of this  
12 discussion is the consideration of the entire  
13 group. What are we doing here? How did we get  
14 here? And as the gentleman before me said, whether  
15 we should rethink the concept before we move  
16 [indiscernible].

17 DR. McCANN: Thank you. Ms. Spotila?

18 MS. SPOTILA: Jennifer Spotila. I don't  
19 think we took time to thank everyone for their  
20 comments, both here in person and in the docket.  
21 There were some personal stories in the docket that  
22 I hope everyone had a chance to read. And I want

1 to thank you. As a fellow person with chronic  
2 pain, it's hard to talk about your personal  
3 situation in public, so I appreciate everyone who  
4 spoke up.

5 I think something that we've missed today is  
6 the voices of people affected on both sides of this  
7 issue. There are really two simultaneous public  
8 health crises, the opioid abuse crisis and the pain  
9 management crisis. And I was actually really  
10 disturbed that PTI confined their information  
11 collection from abusers to internet forums.

12 Why don't you bring people in who have used  
13 these drugs recreationally? Why don't you talk to  
14 them? Why doesn't FDA talked to them? Ask them,  
15 how you use this drug? Have them look at it.  
16 Especially when you have a novel formulation like  
17 we have here with a novel abuse deterrent property,  
18 how would you hack this? What would you try? If  
19 you lost 20 to 30 percent of the gel when you split  
20 it open, are you going to split open another one,  
21 and then what dose are you going to get? We didn't  
22 even get PK on that to see what that would do.

1           So I think that we really have to look at  
2       defeating abuse-deterrent properties as a puzzle  
3       that humans will solve if they are motivated enough  
4       to do so. We need to better understand that, so  
5       you can design your studies to really answer that  
6       question.

7           Then there's the flip side of people with  
8       chronic pain. Again, I was surprised that PTI said  
9       there were no other comparator groups, no other  
10      control groups or pain models besides  
11      osteoarthritis and back pain. I have neither, but  
12      I've been a chronic pain patient for 20 years.  
13      There are abundant models.  
14      There are many kinds of pain. And we need to take  
15      that into consideration when we evaluate these  
16      studies as well, because this isn't going to be  
17      labeled, like others have said, for osteoarthritis.  
18      It's going to be labeled for severe pain from all  
19      sources.

20           What are the barriers to care? How do  
21      people who are on opioids use or misuse their  
22      drugs, and all of the access issues that come with

1 that? Outcomes. You asked a great question,  
2 Dr. Brent, about the outcomes. You should be  
3 taking outcomes throughout the study, after the  
4 study, after termination of the drug. I also was  
5 not persuaded by the statement that these subjects  
6 did not have withdrawal. They would have. That  
7 should have been detected in the studies as one of  
8 the signals.

9 Then there's the access to care issue. I've  
10 had chronic pain for 20 years. I've been in pain  
11 management for 15. I've been on opioids for 10,  
12 safely, and my healthcare has been criminalized to  
13 a certain extent, the barriers that I have to  
14 overcome simply to function with proper medication.  
15 And I'm lucky that I still have access to that.

16 So all of these factors have to play into  
17 the question of safety, efficacy, an  
18 abuse-deterrent potential labeling requirements,  
19 et cetera. It all matters.

20 DR. McCANN: Thank you. I think we're sort  
21 of bleeding into question 3, which we really  
22 haven't discussed yet, which is important to

1 discuss. But we'll just keep that in mind when we  
2 finish up with discussing question number 1.

3 Dr. Ciccarone?

4 DR. CICCARONE: Dan Ciccarone, UCSF. So a  
5 couple of things, quickly. One, kudos to the FDA  
6 for pursuing a scientific evidence base to answer a  
7 very complex set of questions, both clinical, all  
8 the way to public health, and for including public  
9 health into the opioid dilemma.

10 Kudos to the sponsor for coming up with a  
11 clever product. I do have to say, though, just to  
12 bring in some discussion point around question 1,  
13 my research is in the real world. I spend a lot of  
14 time with folks that like to use opioids for  
15 pleasure as part of what I might clinically  
16 describe as opioid-use disorder. They use heroin,  
17 they use fentanyl, they use a whole variety of  
18 products.

19 I watch them prepare products. So when I  
20 see FDA data, category 1 study data, that says that  
21 this product is -- the oxycodone is extractable,  
22 it's very disappointing. And I know there's a

1 dilemma between what sponsor's data has brought in  
2 and your third-party studies, and what the FDA lab  
3 shows, but decoding, without saying anything about  
4 industry secrets, decoding what the solvents are,  
5 what the time is, what the temperature is, it's not  
6 outside of real world. It's not outside of what is  
7 possible in the real world to extract what will  
8 turn out to be 83 percent of the label claim or 29  
9 milligrams of injectable oxycodone, which is a big  
10 dose if you inject it IV.

11 So those are my concerns, which in my mind  
12 starts to topple a claim of abuse deterrence in the  
13 intravenous category. Thank you.

14 DR. McCANN: Great. Awesome. Could we have  
15 a Dr. Nelson again, please?

16 DR. NELSON: Thanks. I had a quick  
17 question -- Lewis Nelson -- maybe for Dr. Hertz.  
18 Apropos to my comment before that less drug release  
19 doesn't necessarily equal less abuse, when the  
20 sponsor gets a label that states that they're going  
21 for a claim of less intranasal and intravenous  
22 abuse, but they're not asking for a label that

1 connotes less oral abuse, what does that actually  
2 mean when we put the drug out there? Because  
3 people are going to know that it's orally abusable.  
4 Right?

5 So I'm not sure I understand the implication  
6 of asking or not asking about label claim when we  
7 know that it's got oral abuse potential. Does that  
8 make sense?

9 DR. HERTZ: I don't know if we've prepared a  
10 section 9.2 to project for this meeting, but the  
11 conclusion for all products, regardless of the  
12 number of routes in which studies support relative  
13 deterrent effects, it still says the product  
14 remains abusable by the oral, nasal, and  
15 intravenous route. So does that complicate the  
16 question?

17 These are not abuse proof. Nobody has  
18 figured that out yet. And because they deliver an  
19 opioid as an analgesic, if you can't manipulate it  
20 at all, you can still just swallow one. So it's  
21 about providing information about the product's  
22 performance, and hopefully someday we'll have

1 sufficient information to see if they are  
2 worthwhile.

3 DR. NELSON: Yes. That answers my question.  
4 I guess what I'm sort of getting at is, in a way,  
5 by only giving two out of these three routes a  
6 label of, quote/unquote "safety," is that a wink  
7 and a nod to the fact that it's actually orally  
8 abusable if people kind of learn how to read  
9 through that? And if we believe the data, which I  
10 think is the most clear, that oral doesn't really  
11 have any abuse prevention -- the others might  
12 maybe, depending on how you want to look at  
13 it -- would we be comfortable releasing this with  
14 any sort of suggestion that it's abuse deterrent  
15 when we know that there's a big hole in that?

16 DR. HERTZ: These are the questions we'd  
17 like you to answer.

18 (Laughter.)

19 DR. McCANN: Dr. Shoben:

20 DR. SHO BEN: Yes. I just wanted to make two  
21 quick comments, I think. One is to say that I  
22 would agree with the comments that have been made

1 about the oral, that I don't think  
2 there's -- there's maybe a suggestion that it's  
3 possibly in the right direction, but it's certainly  
4 not anything that would rise to the level of  
5 abuse-deterrent properties via the oral route,  
6 based on the chewing studies.

7 I do want to make a pitch, I guess, on  
8 behalf of the sponsor, that I do think that their  
9 nasal data is convincing, that it is actually abuse  
10 deterrent from the nasal route, given sort of what  
11 we've done previously and the data that they have  
12 from the abuse potential studies showing lower drug  
13 liking, and take drug again, and things like that.

14 Intravenous data is much harder for me. The  
15 conflicting data between the sponsor's third party  
16 and the FDA makes it hard to know in the real world  
17 how quickly would abusers be able to defeat the  
18 properties, and then how much additional risk is  
19 there from the types of things we saw with Opana in  
20 terms of getting larger volumes of injectable  
21 solutions, and the kinds of things that might  
22 follow from that. But it is certainly not as easy

1 to abuse intravenously; that's just sort of a  
2 standard, like the old school, crush it up with a  
3 spoon and dissolve it in a little bit of water, and  
4 inject. So I'm sort of torn about the intravenous  
5 route.

6 DR. McCANN: Thank you. Thank you for  
7 getting back to the original question also. And  
8 we're going to go with Dr. Goudra.

9 DR. GOUDRA: Basavana Goudra, pain medicine,  
10 anesthesiologist. I think the questions are kind  
11 of twofold here, and many of you have kind of  
12 addressed it. One is kind of both philosophical  
13 and practical, but having worked in both  
14 Europe -- I worked in England and Ireland both and  
15 here -- it's kind of incorrect to compare the two.

16 Just to give an example, if you explain to a  
17 patient what I'm going to do in terms of  
18 anesthesia, patients will tell you, you are the  
19 doctor; do what's right. Such a thing doesn't  
20 happen here.

21 So in terms of patients' tolerance, and in  
22 terms of the whole issue of how they tolerate the

1 pain, how they approach the pain and the patient's  
2 expectations -- and even the physicians' approach  
3 is different, so I don't think we should be  
4 comparing both of them.

5 The second thing is, we're looking at I  
6 guess three things here. And the efficacy was to  
7 deter oral abuse, both nasal and intravenous. I  
8 don't think anybody's asking us to quantify the  
9 amount of data in terms of abuse. I am willing to  
10 accept that oral abuse may not be that much  
11 different, but in terms of nasal and intravenous,  
12 it is. And just going by that, I was looking over,  
13 and in at least one study, almost 19 persons, their  
14 admissions to the ER were because of nasal abuse of  
15 OxyContin. Even if it 15 person [indiscernible]  
16 detriment, for example, it is still very  
17 significant.

18 As it is, I think it's kind of mixed, but  
19 overall, I'm kind of willing to accept definitely  
20 it's a deterrent in terms of nasal and intravenous,  
21 and probably, to a certain extent, oral. In fact,  
22 the bigger concern is regarding its clinical

1 efficacy, whether we should be extrapolating the  
2 results coming from one study in patients with  
3 chronic pain in knee and hip to patients who have  
4 much more intense pain, common being the back ache.  
5 But I guess we cannot expect a company to do  
6 studies in every possible condition, every possible  
7 group.

8 As a result, I'm willing to go by whatever  
9 that's presented to me to make up my mind, as I  
10 stated. Thank you.

11 DR. McCANN: Dr. Arfken?

12 DR. ARFKEN: [Inaudible - off mic].

13 DR. McCANN: Oh, okay. Dr. Terman?

14 DR. TERMAN: Sure. My two cents is I think  
15 that they have shown that there is a deterrence of  
16 nasal abuse and intravenous abuse. Now, how much  
17 deterrence is always a question. It depends how  
18 hard people are willing to try. The oral is,  
19 clearly, they have not, in my opinion, shown  
20 deterrence. And I guarantee that there will never  
21 be a drug where there is complete deterrence since  
22 my patients need to extract that drug in their gut.

1 The phase 3 showed that there was so much  
2 extraction in some of the patients that they quit  
3 taking the drug because no one likes taking opiates  
4 because of all the side effects; that is, the vast  
5 majority of people don't like taking opiates  
6 because of the side effects.

7 I guess I would the FDA, this is not the  
8 first time that this drug has come before the FDA.  
9 According to the sponsor, at least once before, I  
10 think maybe twice, the concerns, deficiencies,  
11 were around commercial manufacturing, which I won't  
12 understand anyway, and nonclinical support, which  
13 it seems like I should  
14 understand, but I don't.

15 Can you tell me what nonclinical support  
16 means?

17 DR. HERTZ: The studies that Dr. Mellon  
18 described are the nonclinical support, in part, and  
19 then the additional work on the excipients, so all  
20 of that material.

21 DR. McCANN: Ms. Robotti?

22 MS. ROBOTTI: I'm going to hold most of my

1 comment for question 3, but I do want to just ask  
2 rhetorically, of what use is there to the doctor  
3 when told that the drug is abuse deterrent for  
4 nasal only? I'm not sure that that's useful  
5 information, unless you've got a patient who has a  
6 history of drug abuse, nasally only; then, here,  
7 try this drug. I don't quite get the usefulness of  
8 that.

9 DR. McCANN: Thank you. Dr. Zibbell?

10 DR. ZIBBELL: Hi. Jon Zibbell, RTI  
11 International. I'm going to save most of my  
12 comments for question 3 as well, but I did just  
13 want to express -- something like Dan, I actually  
14 do community-based research, and I work with a  
15 population of people who abuse these medications.  
16 And it's hard to conceptualize and separate one  
17 route of administration from the rest.

18 One of the things that we learn is that  
19 abuse happens on a continuum, and I would say 90  
20 percent of the people I've spoken with over the  
21 course of 20 years, they start out orally abusing  
22 them and orally taking a medication, not chewing

1       it, just orally taking it.

2               The thing about opioids is you get an  
3       increase in tolerance, the more you use.  People  
4       realize when you break that extended release, it's  
5       going to release more drug, and so people orally  
6       take it.  And then they learned chewing it is going  
7       to release more of the medication, and then you're  
8       getting more of the rush so to speak.  Then you get  
9       up a tolerance to that, and a lot of people  
10      transition to insufflation, smoking or sniffing,  
11      and then injecting.

12              My concern with the oral is the chewing,  
13      really, because it's going to release those  
14      opioids.  We do know that higher doses are at  
15      higher risk for folks for addiction opioid use  
16      disorder, which can also lend itself then to trying  
17      nasal.  If you're going to chew a drug, you're  
18      trying to get more of it.  And kind of separating  
19      out different routes of abuse, if it doesn't tackle  
20      all those, I think it's just problematic for the  
21      real world.

22              It just brings me back the field work I did

1 in Scott county, Indiana, where people reported  
2 there that the OxyContin formulation, the  
3 reformulation, they were sniffers before that, and  
4 they could no longer sniff OxyContin anymore. And  
5 they found Opana, and they couldn't sniff Opana  
6 either, but they could inject it. And there were a  
7 lot of people that reported to me in the field that  
8 they were sniffers, and then with the OxyContin  
9 reformulation, they started to inject. So they  
10 transitioned through different routes of abuse due  
11 to the abuse deterrence.

12 So it's just hard for me. I just want to  
13 express that it's hard to parse out and take away  
14 one form of abuse when opioid-use disorder and  
15 addiction is along a continuum. People traverse  
16 these routes back and forth. I just wanted to make  
17 that comment.

18 DR. McCANN: And we're going to wrap up with  
19 Dr. Meisel, and then I'm going to try to summarize  
20 this discussion.

21 DR. MEISEL: I'll be brief. I just decided  
22 to do a little Google search on the definition of

1 the word "to deter". "Discourage someone from  
2 doing something typically by instilling doubt or  
3 fear of the consequences, and prevent the  
4 occurrence of." And I think it can be pretty clear  
5 that nothing we could do with a oxycodone product  
6 would deter abuse. If somebody's intent is to  
7 abuse it, they'll find a way.

8 DR. McCANN: All right. I'm going to try to  
9 attempt to summarize this. It strikes me that  
10 people answered this question both broadly and  
11 specifically. The broad concern was about the  
12 whole entire concept of abuse deterrence, which may  
13 refer back to question 3 to a certain extent.

14 People were concerned that successful abuse  
15 deterrence can possibly accelerate the transition  
16 to illicit drugs; that it's important to remember  
17 the voices of the affected people, both those that  
18 have the propensity for abuse and those who are  
19 suffering from chronic pain, and what the  
20 implications are of labeling a drug as non-oral  
21 abuse potential, whether that means that people  
22 would realize, well, this you can't inject this

1 drug maybe easily, you can't intranasally use it,  
2 but you sure can abuse it orally.

3 Dr. Meisel in particular has been our word  
4 parser, and he has expressed difficulties with the  
5 phrase "expected to deter abuse," what that exactly  
6 meant. He helped us out with the definition of  
7 abuse and pointed out that the reference materials  
8 used by the sponsor varied quite a bit. So to some  
9 degree, it was difficult to make adequate  
10 comparisons.

11 Then specifically, I think the consensus was  
12 that oral abuse potential was the greatest. There  
13 was the least evidence for deterrence in that  
14 route. Most people felt that this drug, the  
15 sponsor did demonstrate some nasal deterrence. And  
16 the discussion I think was fairly mixed about  
17 whether there's IV drug abuse potential. The FDA  
18 data was quite compelling for several of the people  
19 on the panel.

20 So that's how I summarize it, and I think if  
21 that's all right, we can go on maybe to our second  
22 question.

1           The second question as I read, or read it  
2 before, is fairly specific, and I think we may want  
3 to deal with the specifics of it. So question 2,  
4 please discuss whether there are sufficient data to  
5 support inclusion of language regarding  
6 abuse-deterrent properties in the product label of  
7 REMOXY ER, commenting on support for  
8 abuse-deterrent effects for each of the following  
9 routes of abuse: A oral, B, nasal; C, intravenous.

10           DR. GRIFFIN: Marie Griffin. I'd say no,  
11 yes, no.

12           DR. McCANN: That was a very specific  
13 answer. That's what I asked for.

14           (Laughter.)

15           DR. McCANN: You get what you ask.

16           Dr. Nelson?

17           DR. NELSON: My specific answer is no, no,  
18 no. It really is what I enunciated before, just  
19 clearly oral doesn't have that. Nasal, I'm still  
20 very concerned that the multiple dose issue, again,  
21 less drug released doesn't necessarily equal less  
22 abuse. And intravenous, they just don't have data

1 to show that. It's too conflicting.

2 DR. McCANN: Ms. Spotila?

3 MS. SPOTILA: Jennifer Spotila. At first a  
4 question -- if it was more appropriate to have  
5 asked this morning in closed session, then that's  
6 fine. Can we have any additional information about  
7 the effects of chewing in terms of the experience  
8 of chewing, not pharmacokinetics but the property  
9 of the gel itself? So that's my question, and then  
10 I have an answer to the stated question.

11 DR. McCANN: I don't think we have an answer  
12 to that. We probably should have asked that. It's  
13 a great question. FDA may know more data about  
14 these excipients used in other chewable products.

15 DR. HERTZ: I don't think we can comment on  
16 the experience of chewing.

17 MS. SPOTILA: That's fine. Then for the  
18 question under discussion, apart from labeling that  
19 there are abuse-deterrent properties, we got one  
20 label, I believe, Apadaz, where it was specifically  
21 stated in the label that the studies did not show  
22 abuse-deterrent properties. So can we have some

1 discussion on the flip side of a specific negative  
2 label for abuse deterrent?

3 DR. McCANN: Sharon? Dr. Hertz?

4 DR. HERTZ: Sharon's fine.

5 (Laughter.)

6 DR. HERTZ: Sharon Hertz. What we have  
7 decided, with Apadaz as an example, is that when a  
8 product is designed intended to be abuse deterrent,  
9 and we don't believe there are data to support  
10 those features, but it would otherwise be  
11 reasonable for someone who perhaps followed  
12 development or read our reviews, whatever, to have  
13 thought that this was, we will put in studies so  
14 that people can be fully informed.

15 Does that provide what you were questioning?

16 (Ms. Spotila gestures in the affirmative.)

17 DR. McCANN: Dr. Brent?

18 DR. BRENT: Jeff Brent. Just a fast point.  
19 Oral, clearly not; nasal, somewhat equivocal. I  
20 think there's reasonable data that if we don't look  
21 at deterrence as being absolute, we do see it as  
22 something that sort of makes it a little harder. I

1 would have a huge objection to nasal, although I  
2 agree with Lewis that it's not a huge deterrent.

3 The comment I wanted to make, though, is  
4 more regarding the intravenous. We have to realize  
5 that there are two components to the concerns about  
6 the intravenous; one, which is the relevant one  
7 here, which is the likelihood of releasing drug;  
8 but the second component is also the potential  
9 infusion relatively uncharacterized excipient,  
10 which probably we should discuss under 3. But I  
11 just wanted to be sure we were pretty clear that  
12 they were two separate components to the concerns  
13 about the intravenous.

14 DR. McCANN: Dr. Terman?

15 DR. TERMAN: So again, I am a little bit  
16 more positive about the intravenous just because of  
17 all the information that we saw in the closed  
18 session about all the different parameters that  
19 were done. But even if people did decide that even  
20 just the nasal was worth talking about in the  
21 indication, that the nasal did deter abuse, I think  
22 this a situation where you really would need to

1 point out that the oral route has kind of  
2 demonstrated that it's not abuse deterrent  
3 because -- and not just stay silent on that issue.

4 I am concerned about how little I  
5 heard -- and part of that's my fault for not  
6 asking, but why it is that you can do all those  
7 things without releasing all of the drug, and yet  
8 you can chew it, and you get a very rapid -- I  
9 mean, essentially, it's no longer ER/LA. They  
10 didn't show the figure out past 4 hours, but my  
11 assumption is that it is no longer long acting.  
12 And the question is how long you have to chew it,  
13 which, again, we didn't hear anything about, not  
14 just the chewing is a problem, but what if, as  
15 someone else said, someone just decides to chew it  
16 once or twice, not for five minutes.

17 That is a big concern, particularly if it's  
18 on top of a standard dose several days into -- and  
19 again, I'm not talking about abuse here. I'm  
20 talking about just use, and someone mistakenly,  
21 perhaps for the last time, chews their drug?

22 DR. McCANN: Dr. Hertig?

1 DR. HERTIG: John Hertig, Purdue University.  
2 So to answer this specific question at hand, I'm a  
3 no, yes, and then incredibly complicated, because  
4 there's almost this incremental deterrence that's  
5 happening where it may be incredibly difficult the  
6 first time, but because of things like social media  
7 and websites and the internet, that subsequent  
8 deterrence actually lessens because the way to get  
9 around that is shared. So that's why this becomes  
10 incredibly complex for me.

11 DR. McCANN: So with that, I think will  
12 briefly summarize this question, and then maybe  
13 take a short break. So I asked for specifics. Of  
14 the 1, 2, 3, 4, 5, 6 people that gave specifics, 6  
15 out of 6 said that there's no oral deterrence. 5  
16 out of 6 said there was nasal deterrence. 4 out of  
17 the 6 expressed IV deterrence -- actually, it was 3  
18 out of the 6, and 3 expressed concern about the IV  
19 data, which is probably more like they did not  
20 really think there was enough data to support IV  
21 deterrence.

22 There were also specific concerns expressed

1 about the dangers of injections of excipients that  
2 was not adequately explored by the sponsor. And a  
3 number of people wanted the label to state  
4 explicitly that this drug had no oral deterrence.  
5 And it was also expressed by several people that  
6 they were a lack of chewing studies, that we don't  
7 know what the effects are of chewing for a long  
8 time as opposed to just chomping down once on the  
9 tablet.

10 So with that, I would like to adjourn for 10  
11 minutes for a quick break, and then we'll go to the  
12 third question.

13 (Whereupon, at 3:24 p.m., a recess was  
14 taken.)

15 DR. McCANN: Hello. I'm going to ask  
16 everybody to take their seat now for question  
17 number 3.k

18 Question number 3. The applicant is  
19 requesting approval of REMOXY ER as an analgesic  
20 with properties expected to deter abuse by the  
21 intravenous and intranasal routes. Discuss whether  
22 you have any concerns regarding the impact of

1 REMOXY ER on public health. Take into  
2 consideration its potential effect on the abuse of  
3 extended-release oxycodone, as well as potential  
4 consequences of administration of this product by  
5 unintended routes.

6 If there are no questions or comments  
7 concerning the wording of this question, we will  
8 now open the question to discussion. Dr. Arfken?

9 DR. ARFKEN: Cynthia Arfken. These three  
10 different routes of administration are not just  
11 three different colors. They recognize different  
12 consequences and severity of use. So I have  
13 concerns about the most severe route of  
14 administration not being shown to be a deterrent.  
15 So even though there might be discussion on whether  
16 nasal route is deterred, the whole idea that the IV  
17 route is of great concern to me. So that makes me  
18 very uncomfortable with supporting any indicator  
19 for this.

20 DR. McCANN: Thank you. Dr. Zibbell?

21 DR. ZIBBELL: Jon Zibbell, RTI  
22 International. First of all, I want to say thank

1 you to FDA for having this question. It's a really  
2 important question, and also hard to see into the  
3 future without some postmarket studies as well. In  
4 public health, we often think of primary versus  
5 secondary prevention. And when we think about  
6 people with addictions and opioid-use disorders,  
7 primary prevention is stopping someone from ever  
8 starting, ever taking a medication that might cause  
9 them harm, whether it's orally taking it, whether  
10 it's chewing it, but someone who is a neophyte, is  
11 opiate naive.

12 Secondary prevention is people that already  
13 have an opioid-use disorder, already have an  
14 addiction beyond recreational use, problematic use,  
15 chaotic use; the things that they'll do to  
16 manipulate pharmaceutical medications in order to  
17 abuse them are great.

18 So if we look at both of those, this  
19 absolutely for me doesn't deal with primary  
20 prevention because of its oral aspect. The people  
21 can still take it. And it's not just about the  
22 oral aspect. It's the dose dumping, it's the

1 chewing, it's the interruption of the  
2 extended-release mechanism. I'm guessing  
3 swallowing this, at least from the data, it seems  
4 like that you're going to get your, whatever,  
5 5 milligrams every hour for a period of time, but  
6 chewing it breaks that mechanism, getting some type  
7 of dose dumping, and getting that euphoria, and  
8 getting the trigger in the brain.

9           So the primary prevention thing, I don't  
10 think this deals with that, but the secondary  
11 prevention is another big concern. And one of the  
12 things I've learned from my field work over the  
13 years has been that people that are already  
14 physically dependent and addicted to opioids will  
15 go through great lengths to manipulate products in  
16 order to extract the drug from them in order to  
17 use. And I just brought up Scott County because  
18 that's the most acute in my mind, that I got to see  
19 that really firsthand, the lengths that someone  
20 would go to do that.

21           So I just table the nasal thing because I'm  
22 a little confused about the nasal. The data seems

1 like it could go either way, and there's not a lot  
2 of it. But the injection aspect does give me great  
3 cause for concern. It's hard to make sense of  
4 FDA's position in terms of the data and the  
5 sponsor's, but nevertheless, the chance that it can  
6 be manipulated, and looking actually at the  
7 process, which was 20 to 30 minutes -- a little bit  
8 longer than the patience of most people, but not  
9 too, too long, like a couple hours, the ability to  
10 manipulate that -- in Scott County, what we  
11 found -- and this has been research that we've been  
12 trying to figure out for a long time, what is the  
13 disease risk associated with injecting pills,  
14 manipulating pills?

15           What we found from Scott County was the  
16 volume of solution in liquid that is needed in  
17 order to do that. Give you an example. So the  
18 Opana medication had excipients in it to resist  
19 crushing. Well, people in Scott County found that  
20 if you put that in an oven, and you burn it, you  
21 can interrupt that excipient, and then you're able  
22 to make it malleable, and crush it with your finger

1 or whatever. And then you add water to it, and you  
2 start mixing it up. But you can't just use regular  
3 water like 1 mL in a syringe like you would with  
4 heroin. You need copious amounts of water to  
5 override mostly the hydroxyethyl cellulose.

6 So you put a lot of water in there, and what  
7 that does is it makes a big solution. But the  
8 people in Scott County only have these 1-milliliter  
9 needles, so they had a 5-milliliter solution, a  
10 3-milliliter solution. In order to turn that pill  
11 into an injectable solution that wasn't goopy, add  
12 enough water; it gets liquid enough, and they would  
13 do multiple injections.

14 Really, that's what we believe led to the  
15 spread of disease, because right now you had a  
16 solution that was 3 to 5 mLs, and you had 3 to 5  
17 shots. So you could do all three of those yourself  
18 or you could share them.

19 Those of us on the ground really even  
20 couldn't come up with this. We didn't even foresee  
21 this. And I think what this showed to me is that  
22 if these substances can be manipulated with -- I

1 won't say household products, but citrate is a  
2 pretty easy product to get, or ascorbic acid. And  
3 in California, they already use that to deal with  
4 tar heroin because tar heroin is hard water  
5 soluble, and so you already use the citric or  
6 ascorbic acid.

7           If that can be done in 20 to 30 minutes,  
8 that raises concerns for me, and it raises concerns  
9 like I almost see this as an Opana like product.  
10 You could eat it, you couldn't sniff it, but you  
11 might be able to inject it. So I do have concerns  
12 that this will be manipulated, and it's able to be  
13 extracted, and that we could see similar HIV and  
14 HCV transmissions because we know that if it can be  
15 extracted, people are going to do that. Now,  
16 that's not a huge part of the population, 20,  
17 30 percent of the population, but a large enough  
18 number to raise concern. Thanks.

19           DR. McCANN: Thank you. Ms. Spotila?

20           MS. SPOTILA: Jennifer Spotila. I want to  
21 echo the concern about an Opana-like situation and  
22 tertiary and down-flow effects in terms of spread

1 of disease and other issues. I have a question  
2 about the nasal mode of abuse. We didn't get  
3 pharmacodynamics in the nasal human abuse potential  
4 study for oxy ER, and PTI said that was based on  
5 FDA's advice.

6 Can you comment at all on would that have  
7 made a difference to the signal that we saw  
8 relative to intact REMOXY manipulated and then the  
9 oxy IR?

10 DR. HERTZ: We can't speculate on that.

11 MS. SPOTILA: So you can't speculate. Was  
12 there a reason for telling them to use IR instead  
13 of ER?

14 DR. HERTZ: As we learn about whether or not  
15 a product -- as we learn about the features of  
16 these different products, abuse deterrence is a  
17 relative concept. It's something more difficult  
18 than something else. So the first question is how  
19 does it compare to IR because that's what people  
20 would seek out if they had a choice. Then the  
21 question is, where relevant, according to the  
22 guidance, other active comparators should be

1 included.

2           So if someone had taken only an extended  
3 release, maybe another ADF, and showed it was a  
4 little better, or a little worse, somehow  
5 different, do we know if in that particular  
6 population, in that particular study, there was any  
7 effect? We can show two products or two sets of  
8 data are similar, but we can't necessarily assume  
9 that they are showing an absolute effect.

10           So you need to have the IR for essay  
11 sensitivity to show that it's actually better than  
12 the IR because they might both be the same, and  
13 they might both look as bad as something without  
14 product. And as you have gotten a sense, there are  
15 so many variables in a lot of these studies, that  
16 it's hard to know how to recreate one company  
17 versus another's conditions.

18           So you would say, well, but product x is  
19 already abuse deterrent, so if it's the same, it's  
20 as good, and therefore, my product's abuse  
21 deterrent; except unless you didn't study it  
22 properly, unless you found a different way to

1 defeat it. I mean, there are so many ifs. To  
2 eliminate the ifs, we say use IR.

3 We are always asking for active comparators.  
4 We asked for active competitors in these studies.  
5 We asked for active comparators in efficacy  
6 studies. We push as hard as we can, but people  
7 don't listen. They don't say, okay; they just do  
8 what they feel is best for their individual  
9 development programs. So we need to have some  
10 understanding of the low-side assay sensitivity  
11 even though we'd also like that other side.

12 DR. McCANN: Dr. Goudra?

13 DR. GOUDRA: Basavana Goudra from pain  
14 medicine, anesthesiologist. The question, as an  
15 analgesic, has it got properties that are expected  
16 to deter abuse? I think the answer is absolutely  
17 yes for intravenous and intranasal. How much?  
18 That's probably debatable.

19 The next question is can it worsen IV drug  
20 abuse? Yes, in certain individuals. Maybe they  
21 can probably exploit it for intravenous abuse, but  
22 these two have to be looked at differently,

1       deterrence of intravenous use versus a specific  
2       group of people trying to manipulate it for  
3       intravenous series.

4               The next thing is do we have alternatives to  
5       this. Not many, so we certainly need analgesics.  
6       Opioid analgesics are definitely needed for certain  
7       types of pain, and I certainly think this drug  
8       is -- it's not the holy grail. It's not going to  
9       address everything. It's certainly a step in the  
10      right direction.

11             DR. McCANN: Thank you. Dr. Brown, now.

12             DR. BROWN: Thank you, Dr. McCann.

13             I'd first like to commend the agency for the  
14      good work that they've done over the course of the  
15      last 10 years to try to get this issue right. This  
16      is an incredibly complicated problem, and it's  
17      easy to ask these hard questions that we're asking.  
18      But it shouldn't be thought of as reflecting on the  
19      desire or the hard work that's been put in by every  
20      member of the agency to try to rectify what is a  
21      global population problem.

22             That said, when the agency states that

1 something is abuse deterrent, what they actually  
2 included in the label is a statement that it would  
3 be expected to be abuse deterrent. The question  
4 becomes, is that equivalent to say it is abuse  
5 deterrent? I have a personal belief that most  
6 prescribers, if they look at the labeling at home,  
7 believe that when it says would be expected to be  
8 abuse deterrent, count on it to be abuse deterrent.  
9 Now, the agency doesn't believe that it is abuse  
10 deterrent until we get all of the postmarketing  
11 data, which we cannot derive from our friends in  
12 industry.

13 The sponsor of this, -- or the agency  
14 wonders if we have concerns regarding the impact of  
15 REMOXY ER on the public health, and I have  
16 substantial problems with the impact on the public  
17 health. And ,any of the folks that have spoken  
18 before me have very eloquently considered those.  
19 But one potential effect is putting another one of  
20 the ADFs or another opioid compound on the market  
21 has the potential effect of making a statement that  
22 the agency does not believe that there is a

1       problem. And I think that is a problem or an issue  
2       that the agency has consider very closely in their  
3       overall discussions of what to do about this  
4       particular opioid formulation and what to do about  
5       the further formulations.

6               The potential effect on abuse of  
7       extended-release oxycodone, as well as the  
8       potential consequences of administering these  
9       products, are being played out now and have been  
10      demonstrated well. The report by the National  
11      Academy of Medicine asked very eloquently for the  
12      agency to determine whether or not there needs to  
13      be reconsideration of the global mechanism for  
14      defining what is safe and what is not, specifically  
15      with opioids, using the word "exceptionally"  
16      [indiscernible] when describing these drugs. I  
17      happen to concur with them.

18             So I guess that's the end to my diatribe,  
19      but I would think the agency, and I would also like  
20      to thank Dr. Mary Ellen McCann for being so  
21      eloquent today in herding rabbits.

22             DR. McCANN: Thank you, Dr. Brown.

1 Dr. Meisel?

2 DR. MEISEL: Steve Meisel. Two points, on  
3 this question anyway. To sort of echo what  
4 Dr. Brown was talking about or maybe elaborate it  
5 or say it a different way, when these things are  
6 labeled as abuse deterrent, there could be a false  
7 sense of security on the part of the prescribing  
8 and consuming population, that these really are  
9 abuse preventing, and that they're safer to use  
10 than they might otherwise be.

11 I don't know what the marketing or the  
12 experience with labeling is like in Europe or other  
13 countries for products like this, but it may well  
14 be that one of public health impacts of this  
15 product, as well as OxyContin for that matter and  
16 the others, is that it provides a false sense of  
17 security, and we end up prescribing more of these  
18 to more people than we might otherwise if they  
19 weren't labeled as abuse deterrent. I think we  
20 just have to keep that in mind. I don't think  
21 there's an answer to that, but I think we have to  
22 recognize that potential.

1           Several people have mentioned this before,  
2           and we can't lose sight of the fact a  
3           potentially -- well, the uninvestigated risks of  
4           the excipients when given intravenously or  
5           elsewhere. The agency did comment that their  
6           toxicology studies were pretty okay with this  
7           stuff, but I was less than satisfied with the data  
8           that was presented to us, that these items when  
9           given either safely by intent or unsafely by  
10          intravenous or other kinds of routes, wouldn't  
11          cause unintended consequences. And I think that's  
12          an area that needs to be further explored before we  
13          could fully understand the public health impact.

14                 DR. McCANN: Thank you. Dr. Ciccarone?

15                 DR. CICCARONE: Thank you. Dan Ciccarone,  
16          UCSF. Given the question around public health  
17          implications, I have two disease categories that  
18          I'm worried about with this drug. One is  
19          blood-borne virus transmission, hepatitis C and  
20          HIV, and the other is vein loss leading to a whole  
21          variety of conditions. I want to echo what  
22          Ms. Spotila and Dr. Zibbell have brought up, and

1 that is the Opana-like potential characteristics  
2 here that this drug, if extracted using the FDA  
3 category 1 study results, will result in a -- I  
4 know the FDA wants to call this low volume, but in  
5 the real world, a moderate to high volume injection  
6 solution.

7 Dr. Zibbell and colleagues' study in Scott  
8 County, Indiana showed that multiple injections per  
9 dose, per desired dose of a drug, led to a sharing  
10 situation, led to a high-risk blood-borne virus  
11 transmission situation, and we all know the outcome  
12 of that. That work has been published.

13 If these volumes -- again, going to the FDA  
14 data, I'm concerned about multiple injections per  
15 episode, HIV. I'm also concerned about -- without  
16 divulging what the solvent is, I am concerned about  
17 the acidity of the compound as it exists, but also  
18 as it's dissolved, according to the FDA study.

19 There are places in the world that use acid to  
20 dissolve heroin. They use acid to dissolve pills.  
21 In those places that use acid to dissolve heroin  
22 and/or pills, they have a tremendous problem.,

1 public health problem, with vein loss among the  
2 users who inject.

3           Vein loss leads to skin and soft tissue  
4 infections. It also leads to more dangerous routes  
5 of injection. You go from peripheral veins to  
6 central venous to leg veins and neck veins, which  
7 have -- I can leave it to your imagination -- very  
8 potentially disastrous clinical implications, one  
9 of which is happening in the UK right now, which is  
10 about to hit press. And that is a renal disease  
11 due to immunological burden from skin and  
12 soft-tissue infections due to vein loss. They're  
13 seeing a rise in amyloidosis and other renal  
14 failure problems.

15           I would hate to see us five years down the  
16 road, with postmarketing surveillance, saying, hmm,  
17 I wonder where all the renal disease came among the  
18 injection drug users, what caused that. We don't  
19 know, and we don't know with this drug. I'm just  
20 raising it as a hypothetical, given the discussion  
21 question about public health consequences.

22           DR. McCANN: Are there any more comments?

1 Dr. Terman?

2 DR. TERMAN: Sure. So as a pain doc who  
3 also is licensed to do some addiction medicine,  
4 this is obviously a bias of mine, to think that  
5 we're going to ever have a compound, which is truly  
6 abuse deterrent across all routes, it just doesn't  
7 strike me as very realistic. So my public health  
8 issues are going to be in the world of pain. Can  
9 this drug, the impact of this drug on public  
10 health, improve pain? And the phase 3 suggested  
11 that it can help people with pain, those that don't  
12 drop out of the study, about twice as much as  
13 placebo. Despite all the talk about withdrawal  
14 concerns, in fact, the people that titrated down to  
15 placebo actually improved their pain from the time  
16 they started titrating down.

17 So I do think that that can help pain, based  
18 on the data that was presented, and it does have  
19 pharmacokinetics that wasn't really talked about in  
20 detail here, that would, in terms of peak to trough  
21 differences, might actually improve things, might  
22 actually suggest that the drug, unlike other

1 long-acting drugs, might actually last the amount  
2 of time that it's approved for.

3           Nonetheless, I am concerned about this  
4 chewing and whether that might accidentally take  
5 place, accidentally in people trying to take it for  
6 the right reasons. So I am concerned about public  
7 health in that way that offsets improved  
8 pharmacokinetics in my mind.

9           DR. McCANN: So I guess it's time to try to  
10 summarize a very broad question. I think I'll  
11 start with the last comment. The belief is that  
12 this drug does help with pain. And another member  
13 felt it did deter IV and intranasal use; although a  
14 number of people commented on the lack of  
15 information about the nasal route pharmacodynamics.

16           There are also concerns about misuse of this  
17 drug in patients who are trying to use it correctly  
18 with the fact that they may chew the drug and  
19 inadvertently get high doses. Of the three routes  
20 of administration, people were most concerned about  
21 the intravenous route. The concern is that you may  
22 get excipients with this route; that it's the root

1 where the testing between the FDA and the sponsor  
2 differed the most; and then there's a belief that  
3 people who are abusers are going to go through any  
4 number of steps to get the drug if they decide they  
5 need it, so we have to worry about that.

6           Somebody brought up very eloquently the  
7 differences between primary prevention and  
8 secondary prevention, and pointed out that this  
9 would not be a drug that would be useful for  
10 primary prevention because you can just chew the  
11 drug and get yourself high that way. In terms of  
12 secondary prevention, this particular individual is  
13 not hopeful that this drug would be deterrent to  
14 somebody who was determined to get IV use of this  
15 drug.

16           Then there was also -- which echoes the  
17 discussion with question 1 -- the whole concept of  
18 abuse deterrence and does it have unintended  
19 consequences; the idea of putting in a whole bunch  
20 of excipients when you know a certain small  
21 percentage of people are going to defeat the drug  
22 and therefore get much sicker with the effects of

1 the excipients; and that we don't really have  
2 adequate studies of the excipients for this drug,  
3 for use with IV medication, and probably don't have  
4 enough information about the effects of chronic use  
5 orally of this drug used appropriately in terms of  
6 the excipients.

7 A number of people also brought up the issue  
8 that when you use the FDA's -- called it recipe,  
9 but extraction method, that you're left with a  
10 fairly large volume of fluid. So it is very  
11 tempting for abusers to share the drug, and  
12 therefore we need to worry about blood-borne  
13 pathogens, as well as vein loss, peripheral  
14 infections, and possibly leading all the way to  
15 renal damage.

16 Does that cover it for people? Dr. Meisel?

17 DR. MEISEL: Just one additional point.  
18 Steve Meisel. There's been a lot of discussion  
19 about the bolus effect upon chewing this product,  
20 and that's true. But I just want to remind people  
21 that any sustained release product, whether it's an  
22 antihypertensive or drug like this, or any other

1 sort of pharmaceutical, if you start chewing it up,  
2 you destroy the sustained-release component of it,  
3 and you can end up with a bolus with bad effects,  
4 potentially bad effects.

5 So that is something that's inherent to the  
6 fact that it's a sustained-release product and not  
7 necessarily a mark against this drug.

8 DR. McCANN: All right. So now we're on to  
9 the voting part of the day. If there's no further  
10 discussion on this question, we'll now begin the  
11 voting process. Please press your button on your  
12 microphone that corresponds to your vote.

13 I've got to read the question first. Sorry.

14 (Laughter.)

15 DR. McCANN: Question number 4, based on the  
16 data presented and the discussions about the data,  
17 does the efficacy, safety, and risk-benefit profile  
18 of REMOXY ER support the approval of its  
19 application?

20 I haven't told you how to vote, though, yet.  
21 You will be using an electronic voting system for  
22 the meeting. Once we begin the vote, the buttons

1 will start flashing and will continue to flash even  
2 after you've entered your vote. Please press the  
3 button firmly that corresponds to your vote. If  
4 you are unsure of your vote or you wish to change  
5 your vote, you may press the corresponding button  
6 until the vote is closed.

7 After everyone has completed their vote, the  
8 vote will be locked in. The vote will then be  
9 displayed on the screen. The DFO will read the  
10 vote from the screen into the record. Next, we  
11 will go around the room, and each individual who  
12 voted will state their name and vote into the  
13 record. You can also state the reason why you  
14 voted as you did if you want to. We will continue  
15 in the same manner until all questions have been  
16 answered or discussed.

17 So we're ready to vote, right? Are there  
18 any questions about that process?

19 (No response.)

20 DR. McCANN: So if there is no further  
21 discussion on this question, we will now begin the  
22 voting process. Please press the button on your

1 microphone that corresponds to your vote. You will  
2 have approximately 20 seconds to vote. Please  
3 press the button firmly. After you've made your  
4 selection, the light may continue to flash. If  
5 you're unsure of your vote or you wish to change  
6 your vote, please press the corresponding button  
7 again before the vote is closed.

8 (Voting.)

9 DR. McCANN: Did everybody vote? One  
10 person's abstaining. So if you want to abstain,  
11 you have to hit the abstain button. So has  
12 everybody voted?

13 Everyone has voted. The vote is now  
14 complete. Now that the vote is complete, we will  
15 go around the table and have -- sorry.

16 DR. WANG: For the record, for question 4,  
17 we have 3 yeses, 14 noes, and zero abstain.

18 DR. McCANN: Now that the vote is complete,  
19 we will go around the table and have everyone who  
20 voted state their name, vote, and if you want to,  
21 you can state the reason why you voted as you did  
22 into the record. We're going to start on my right,

1 so that would be Dr. Arfken, I believe.

2 DR. ARKFEN: Cynthia Arfken. I voted no  
3 because I was very concerned about the safety.  
4 There were certain questions that were left  
5 unanswered, but more importantly about the public  
6 health benefit.

7 DR. CICCARONE: Dan Ciccarone, UCSF> I  
8 voted no, given the FDA lab category 1 study  
9 results on extractability. If the FDA lab can do  
10 it, then it will be extractable in the real world.  
11 And I'm concerned about the public health  
12 consequences.

13 DR. ZIBBELL: Jon Zibbell, RTI  
14 International. I voted no. I do believe that we  
15 need safer opioid medications, but given the data  
16 presented, especially around oral and injection  
17 data, combined with the public health risks,  
18 specifically around primary and secondary  
19 prevention, I just couldn't say yes.

20 DR. GOUDRA: Basavana Goudra from pain  
21 medicine. I did vote yes. I think most of the  
22 reasons are kind of elaborated during the

1 discussion. I think the biggest factor is that  
2 there are no other real alternatives, and this at  
3 least addresses some of the concerns. And for that  
4 reason alone, it should be approved. Thank you.

5 DR. SHO BEN: Abby Shoben. I voted no. For  
6 me, it sort of came out to the benefit to risk  
7 aspect, that the benefit here is potentially  
8 another abuse-deterrent opioid that would have  
9 abusable [indiscernible] properties. And that  
10 would, in theory, put another barrier to potential  
11 abuse on the market. But with these data, compared  
12 to other abuse-deterrent drugs that are already out  
13 there and the potential risk of creating another  
14 type of Opana situation, the unknown risks  
15 outweighed any potential incremental benefit of  
16 adding another abuse-deterrent opioid.

17 DR. ZELTZER: Lonnie Zeltzer, UCLA. I voted  
18 no because while the only area that had some  
19 convincing data in terms of positive benefit was  
20 the intranasal route, I think the public health  
21 risk of, in particular, the large volume for IV use  
22 would create I think more risk than the overall

1 benefit of approval.

2 DR. GRIFFIN: Marie Griffin. I voted no  
3 mainly based on the data on IV use or the potential  
4 for IV use. I also think the standard for some of  
5 these efficacy trials really needs to change  
6 because our concept of risk of these drugs is  
7 different now than when the drugs were originally  
8 licensed.

9 So I think the data that we saw on safety  
10 and efficacy was really not up to par for -- it  
11 certainly wouldn't be for a new drug. But I think  
12 we need to think about this in a different way, in  
13 a public health way. And I don't think we saw a  
14 lot of evidence for long-term safety.

15 MS. ROBOTTI: I'm Suzanne Robotti. I voted  
16 no. I've sat on this panel for just over a year,  
17 and I've sat on at least five different opioid  
18 anti-abuse drug reviews. And I've learned that any  
19 drug can be abused by a determined addict, as has  
20 been said here before. And therefore, to me, the  
21 primary goal is to deter the initiation of abuse.  
22 The fact that chewing can release the opioid at a

1 high level, any abuse to me by a nasal and IV is a  
2 secondary concern. That said, I sat on the Opana  
3 panel, and that was a terrible, unforeseen outcome  
4 that we need to avoid if there's any foreshadowing  
5 of it here.

6 On the public health level, we also need to  
7 slow initial use of opioids for pain management in  
8 general. We need to emphasize to the opioid-naive  
9 patient that the side effects for opioids used  
10 appropriately as prescribed, the side effects are  
11 significant and uncomfortable. And we need as a  
12 society to make access to alternatives affordable  
13 and realistic whenever possible.

14 MS. SPOTILA: Jennifer Spotila, patient  
15 representative. I voted no because I think the  
16 risk of oral and IV misuse and abuse, both to those  
17 individuals and to public health, as well as the  
18 risk of creating a false sense of safety, those  
19 outweighed the benefits of possible nasal  
20 deterrence and also the benefits to patients in  
21 pain management.

22 DR. McCANN: Mary Ellen McCann. I voted

1       yes. I think there was evidence for nasal and IV  
2       deterrence.

3               DR. McCANN: Dr. Brown, we're ready for your  
4       comments.

5               DR. BROWN: I voted no because of the public  
6       health implication. I'd just like to comment that  
7       for patients that have chronic pain, we must offer  
8       solutions. But we don't improve the lives of  
9       patients by offering bad solutions. And in this  
10      and other circumstances like it, that is what I  
11      fear that we are doing.

12              DR. McCANN: Thank you.

13              DR. MEISEL: Steve Meisel. I reluctantly  
14      voted no. In some respects, I wanted to vote yes  
15      because I think the applicant met its burden of  
16      evidence for abuse deterrence for intravenous and  
17      intranasal. I think the intravenous, despite the  
18      FDA's data, the syringeability, it's a deterrence.  
19      It's maybe not the perfect deterrence, but it is a  
20      deterrence. But at the end of the day, I don't  
21      think any of these products are really a deterrent,  
22      and I wonder if OxyContin, with its current

1 formulation, was submitted today, whether we would  
2 approve that labeling as abuse deterrence. And my  
3 guess is we'd have the same questions today with  
4 OxyContin as we do with this product.

5 With that in mind, I would challenge the  
6 agency to rethink the entire pathway of abuse  
7 deterrence, the guidance document, the  
8 encouragement of vendors to come up with products  
9 like this, because I'm not convinced that we'll  
10 ever see a product that meets the criteria that's  
11 been articulated here today. And I would also  
12 challenge the agency to consider a process to  
13 reevaluate the approved labeling for OxyContin as a  
14 product with abuse-deterrent properties.

15 DR. NELSON: Lewis Nelson, and I voted no.  
16 I think that's not a surprise based on my previous  
17 comments, which I won't repeat. I do have concerns  
18 about the credibility of the abuse deterrence that  
19 they were able to show, the sponsor was able to  
20 show. And of in an unpopular way with the FDA, I  
21 don't really support the efficacy studies that are  
22 being done to show the benefit, the beneficial

1 effects, of chronic opioid use to manage pain. I'm  
2 not convinced that these enriched enrollment and  
3 controlled, randomized withdrawal studies are  
4 adequate given the change in what we understand now  
5 to be the risks of using opioids and the  
6 development of worsening progressive chronic pain  
7 due the hyperalgesia and dependence, and other  
8 long-term use disorders that we seem to be  
9 grappling with in this country.

10 So I'd be very concerned the messaging  
11 around the abuse deterrence and the harm reduction  
12 effects of these opioids if they were approved.  
13 And I think we have to deal with this with the  
14 others that are out there because the message that  
15 people are getting with abuse deterrence is safe,  
16 and I'm just not really sure that's what we're  
17 intending people to hear, whether it's the public  
18 or the medical community. So for those reasons and  
19 others, I voted no.

20 DR. PRISINZANO: Tom Prisinzano. I voted  
21 yes. I felt that the sponsor had met the criteria,  
22 at least for abuse deterrence, in terms of

1 intravenous as well as that for nasal. I think  
2 oral is always going to be a problem in this  
3 particular case. And I thought we're in desperate  
4 need of things for chronic pain, and I thought they  
5 showed, at least the data, that it was effective in  
6 treatment of pain.

7 DR. TERMAN: Greg Terman. I voted no, and  
8 I, too, am very concerned about abuse deterrence.  
9 And I realize that tamper resistant sounds more  
10 like packaging than a drug. But that's really what  
11 we're doing here, is talking about tamper resistant  
12 product. And to think that we can stop abuse by  
13 making it difficult to extract out of 15 different  
14 solvents or can inject through a bunch of different  
15 needles is not what I know about addiction. And  
16 people will pursue their drug of choice. And if  
17 they can't get it here, they'll get it from Chin,  
18 even sometimes in pill form.

19 But because we put so much emphasis on abuse  
20 deterrence, I think the obvious studies of how much  
21 chewing needed to take place to unleash this acute,  
22 this immediate-release effect, seemed to be

1 completely ignored. So I can't really think about  
2 risks and benefits because I don't know what that  
3 risk is; someone trying to do the right thing and  
4 biting into a capsule.

5 DR. BRENT: Jeffrey Brent here. I voted no,  
6 and I did so for some minor reasons and for some  
7 major reasons. To keep my remarks very succinct,  
8 it's late in the day, to say that, for one thing,  
9 I'm not even sure we would need this drug. And  
10 even if it was the perfect drug, whether it really  
11 would be a great addition to our public health  
12 arsenal. Perhaps if it was the perfect drug, as it  
13 was intended to be, we can get rid of OxyContin and  
14 substitute this, and it might work better. But  
15 other than that, I'm not sure it would really be  
16 necessary to have.

17 As I mentioned before, I'm always concerned  
18 that if it is truly an abuse-deterrent medication,  
19 it's going to enhance our experience of people then  
20 turning to other forms of opioids, and particularly  
21 intravenous opioids like heroin.

22 On a more specific level, I did have

1 concerns about the uncharacterized toxicology of  
2 excipients with IV use. I think that's a very  
3 easily remedied problem. To characterize something  
4 like that is quite easy. It's just standard  
5 run-of-the-mill toxicology testing, but at this  
6 point, I certainly didn't feel comfortable  
7 approving the drug.

8           Then lastly, it's not a great deterrent  
9 orally. It's not a great deterrent intravenously.  
10 It's a so-so deterrent nasally. So it really  
11 doesn't add that much. I will say I applaud the  
12 FDA's efforts in trying to encourage  
13 abuse-deterrent medications. I think they do play  
14 a role. Maybe this drug will come back into better  
15 form at some later point, but at this point I find  
16 it not approvable.

17           DR. HERTIG: John Hertig. I also voted no,  
18 and I think ultimately we need to do better, both  
19 for our patients with chronic pain, as well as  
20 those who struggle with abuse. I do applaud the  
21 sponsor for being innovative and taking a step in  
22 the right direction and really appreciated those

1 efforts. But ultimately, when I'm balancing the  
2 risk-benefit, and the availability of some similar  
3 options that are currently on the market, compared  
4 to the possible public health impact for me, it was  
5 a no.

6 DR. McCANN: Before we adjourn, are there  
7 last comments for the FDA?

8 DR. HERTZ: I just want to, one last time  
9 for today, thank you all for coming to provide us  
10 with advice, taking time from your busy schedules.  
11 It's greatly appreciated it.

12 **Adjournment**

13 DR. McCANN: Thank you. We will now adjourn  
14 the meeting. Panel members, please leave your name  
15 badge here on the table so that it can be recycled.  
16 Please also take all your personal belongings with  
17 you, as the room is cleaned at the end of the  
18 meeting day. Meeting materials left on the table  
19 will be disposed of. Thank you.

20 (Whereupon, at 4:22 p.m., the open session  
21 was adjourned.)

22