1 FOOD AND DRUG ADMINISTRATION

2 CENTER FOR DRUG EVALUATION AND RESEARCH

3

4

5 DRUG SAFETY AND RISK MANAGEMENT

6 ADVISORY COMMITTEE (DSaRM)

7

8

9 THURSDAY, JANUARY 24, 2013

10 8:00 a.m. to 5:50 p.m.

11

12

13

14 FDA White Oak Campus

15 Building 31, The Great Room

16 White Oak Conference Center

17 Silver Spring, Maryland

18

19

20

21

22

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER**

3 **(Non-Voting)**

4 **Kristina A. Toliver, PharmD**

5 Division of Advisory Committee and Consultant

6 Management

7 Office of Executive Programs Center for Drug

8 Evaluation and Research

9 **DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

10 **MEMBERS (VOTING)**

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12 **William Cooper, MD, MPH**

13 Professor of Pediatrics and Preventive Medicine

14 Departments of Pediatrics and Preventive Medicine

15 Vanderbilt University School of Medicine

16 Nashville, Tennessee

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21 Harvard School of Public Health

22 Boston, Massachusetts

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2 ***(Consumer Representative)***

3 Clinical Associate Professor of Pediatrics

4 Department of Pediatrics, Division of Developmental

5 Behavioral Pediatrics

6 NYU School of Medicine

7 New York, New York

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9 **Peter Kaboli, MD**

10 Associate Professor, Department of Internal

11 Medicine

12 University of Iowa Carver College of Medicine,

13 Iowa City Veterans Administration Medical Center

14 Iowa City, Iowa

15

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20 University of Colorado, Anschutz Medical Campus

21 Colorado School of Public Health

22 Aurora, Colorado

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4 Department of Emergency Medicine
5 Perelman School of Medicine at the University of
6 Pennsylvania
7 Philadelphia, Pennsylvania
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9 **Marjorie Shaw Phillips, MS, RPh, FASHP**
10 Pharmacy Coordinator, Clinical Research and
11 Education
12 Georgia Health Sciences Pharmacy
13 Augusta, Georgia
14
15 **Maria Suarez-Almazor, MD, PhD**
16 Barnts Family Distinguished Professor
17 University of Texas
18 MD Anderson Cancer Center
19 Houston, Texas
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1 **T. Mark Woods, PharmD**
2 Clinical Coordinator and Residency Program Director
3 Pharmacy Department
4 Saint Luke's Hospital
5 Kansas City, Missouri
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7 **ACTING INDUSTRY REPRESENTATIVE TO THE DRUG SAFETY**
8 **AND RISK MANAGEMENT ADVISORY COMMITTEE (NON-VOTING)**
9 **Jose M. Vega, MD**
10 ***(Acting Industry Representative)***
11 Vice President,
12 Amgen Global Safety
13 Miami, Florida
14
15 **TEMPORARY MEMBERS (VOTING)**
16 **Emilia Bagiella, PhD**
17 Professor
18 Center for Biostatistics
19 Department of Health Evidence and Policy
20 Mount Sinai School of Medicine
21 New York, New York
22

1 **Jan F. Chambers**
2 President/Founder
3 National Fibromyalgia & Chronic Pain Association
4 Logan, Utah
5
6 **Stephanie Crawford, PhD, MPH**
7 Associate Professor and Associate Head
8 Department of Pharmacy Administration
9 University of Illinois at Chicago
10 Chicago, Illinois
11
12 **Richard A. Denisco, MD, MPH**
13 Medical Officer
14 Division of Epidemiology, Services and Prevention
15 Research
16 National Institute on Drug Abuse
17 Bethesda, Maryland
18
19 **Angela Gravois**
20 ***(Patient Representative)***
21 Picayune, Mississippi
22

1 **Christopher Jones, PharmD, MPH**
2 Health Scientist
3 Division of Unintentional Injury Prevention
4 Centers for Disease Control and Prevention
5 Atlanta, Georgia
6
7 **Winifred Landis, RPh, CDE, FAPhA**
8 Pharmacist
9 Certified Diabetes Educator
10 CVS/Caremark Pharmacy
11 Lafayette, Indiana
12
13 **Karl A. Lorenz, MD, MSHS**
14 Director, Veterans Affairs Comprehensive End of
15 Life Care (CELC) Palliative Care Quality
16 Improvement Resource Center (QuIRC)
17 VA Greater Los Angeles Healthcare System
18 Los Angeles, California
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1 **Jane C. Maxwell, PhD**
2 Senior Research Scientist
3 Addiction Research Institute
4 Center for Social Work Research
5 The University of Texas at Austin
6 Austin, Texas
7
8 **Rose May, CRNP**
9 Pulmonary Medicine Consult
10 Pulmonary Hypertension Clinic
11 National Heart Lung Blood Institute,
12 Cardiology and Pulmonary Branch
13 National Institutes of Health
14 Bethesda, Maryland
15
16 **Laura McNicholas, MD, PhD**
17 Clinical Associate Professor of Psychiatry
18 Center for Studies of Addiction
19 University of Pennsylvania School of Medicine
20 Philadelphia, Pennsylvania
21
22

1 **John Mendelson, MD**
2 Senior Scientist, Addiction and Pharmacology
3 Research Laboratory California Pacific Medical
4 Center Research Institute St Luke's Hospital San
5 Francisco, California
6
7 **Melinda Moore, PA-C**
8 Physician Assistant-Certified
9 Space City Pain Specialist
10 Webster, Texas
11
12 **Lewis Nelson, MD**
13 Professor of Emergency Medicine Director,
14 Fellowship in Medical Toxicology New York
15 University School of Medicine
16 New York, New York
17
18 **Mary Ellen Olbrisch, PhD, ABPP** Professor of
19 Psychiatry and Surgery Department of Psychiatry
20 Virginia Commonwealth University Richmond, Virginia
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22

1 **Linda Simoni-Wastila, BSPharm, MSPH, PhD**
2 Professor
3 Vice Chair of Research
4 Department of Pharmaceutical Health Services
5 Research
6 University of Maryland School of Pharmacy
7 Baltimore, Maryland
8
9 **Robert G. Smith, DPM, MSc, RPh, CPed**
10 Clinical Assistant Professor of Podiatric Medicine
11 and Surgery
12 Western University of Health Sciences/College of
13 Podiatric Medicine
14 Pomona, California
15
16 **James H. Woods, PhD**
17 ***(Acting Chairperson)***
18 Professor
19 Department of Pharmacology
20 University of Michigan Medical School
21 Ann Arbor, Michigan
22

1 **Michael Yesenko**

2 ***(Patient Representative)***

3 Brookeville, Maryland

4

5 **Robert W. Zaayer, PA-C**

6 Director

7 Physician Extender Services: Emergency Department

8 Premier Physician Services / Premier Health Care

9 Services / New Century Physicians, Inc. Dayton,

10 Ohio

11

12 **GUEST SPEAKERS (NON-VOTING, PRESENTING ONLY)**

13 **Eric Lavonas, MD**

14 Associate Director

15 Rocky Mountain Poison and Drug Center

16 Denver, Colorado

17

18 **Kevin L. Zacharoff, MD, FACPE, FACIP, FAAP**

19 Vice President of Medical Affairs

20 Inflexxion, Inc

21 Old Field, New York

22

1 **SPEAKERS (NON-VOTING, PRESENTING ONLY)**
2 **Edward Michna, MD**
3 Director, Pain Trials Center
4 Brigham and Women's Hospital
5 Chestnut Hill, Massachusetts
6
7 **Sharon Walsh, PhD**
8 Professor of Behavioral Science, Psychiatry and
9 Director of the Center on Drug Alcohol and Research
10 University of Kentucky
11 Lexington, Kentucky
12
13 **FDA PARTICIPANTS (Non-Voting)**
14 **Michael Klein, PhD**
15 Director
16 Controlled Substance Staff
17 CDER, FDA
18
19
20
21
22

1 **Bob Rappaport, MD**
2 Director
3 Division of Anesthesia, Analgesia, and Addiction
4 Products
5 CDER, FDA
6
7 **Judy Staffa, PhD, RPh**
8 Director
9 Division of Epidemiology II
10 Office of Surveillance and Epidemiology
11 CDER, FDA
12
13 **Douglas Throckmorton, MD**
14 Deputy Director for Regulatory Programs
15 CDER, FDA
16
17
18
19
20
21
22

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

2 (8:03 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. J. WOODS: Good morning. I would first
6 like to remind everyone present to turn off your
7 cell phones, BlackBerries, or anything else you
8 brought with you. That might be a good idea, if
9 you haven't already done so. And I would like to
10 identify the press contact, Ms. Morgan Liscinsky,
11 if she's here.
12 She is, and she's standing up back there for
13 everyone. Thank you.
14 Good morning. My name is James Woods, and
15 I'm the acting chairperson for this meeting for the
16 Drug Safety and Risk Management Advisory Committee.
17 I'll now call the meeting of the drug safety and
18 risk management advisory committee to order.
19 We'll go around the room, and please
20 introduce yourself. I will start with the FDA and
21 Dr. Douglas Throckmorton.
22 DR. THROCKMORTON: Good morning. I'm

1 Dr. Throckmorton. I'm the deputy director for
2 regulatory programs, Center for Drugs, FDA.
3 DR. KLEIN: I'm Michael Klein, director of
4 the controlled substance staff in the Center of
5 Drugs of FDA.
6 DR. RAPPAPORT: Bob Rappaport, director of
7 the Division of Anesthesia, Analgesia and Addiction
8 Products.
9 DR. STAFFA: Judy Staffa, director of the
10 Division of Epidemiology II in the Office of
11 Surveillance and Epidemiology at CDER, FDA.
12 DR. MAXWELL: I am Jane Maxwell. I'm an
13 epidemiologist with the University of Texas in
14 Austin.
15 DR. NELSON: I'm Lewis Nelson. I'm an
16 emergency physician and a medical toxicologist at
17 New York University School of Medicine.
18 MS. LANDIS: Good morning. I'm Winnie
19 Landis. I'm a community pharmacist from Lafayette,
20 Indiana.
21 DR. BAGIELLA: Good morning. I'm Emilia
22 Bagiella. I'm a professor of biostatistics at

1 Mount Sinai School of Medicine.
2 MS. CHAMBERS: Good morning. Jan Chambers,
3 president of the National Fibromyalgia and Chronic
4 Pain Association.
5 MR. ZAAYER: Good morning. I'm Bob Zaayer,
6 a practicing emergency medicine PA and director of
7 physician extender services for Premier Physician
8 Services in Ohio.
9 DR. KABOLI: I'm Peter Kaboli. I'm a
10 hospitalist and a health services researcher at the
11 Iowa City VA Medical Center.
12 DR. PERRONE: Good morning. I'm Jeanmarie
13 Perrone. I'm the director of medical toxicology at
14 the University of Pennsylvania.
15 MS. PHILLIPS: Marjorie Shaw Phillips,
16 pharmacy coordinator at Georgia Health Sciences
17 Medical Center and professor at University of
18 Georgia College of Pharmacy.
19 DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz,
20 associate professor of epidemiology, Harvard School
21 of Public Health in Boston.
22 DR. M. WOODS: Good morning. My name is

1 Mark Woods. I'm the clinical coordinator and
2 residency program director in the pharmacy
3 department at St. Luke's Hospital in Kansas City,
4 Missouri.
5 CMDR TOLIVER: Kristina Toliver, designated
6 federal officer, Drug Safety and Risk Management
7 Advisory Committee.
8 DR. J. WOODS: For those of you with short
9 attention spans, my name is James Woods. I'm
10 professor of pharmacology and psychology at the
11 University of Michigan.
12 DR. MORRATO: Good morning. I'm Elaine
13 Morrato, and I'm an epidemiologist in the
14 department of health systems management and policy
15 at the Colorado School of Public Health, University
16 of Colorado.
17 DR. COOPER: I'm William Cooper. I'm
18 professor of pediatrics and preventive medicine at
19 Vanderbilt University in Nashville, Tennessee. I'm
20 a pediatrician and a pharmacoepidemiologist.
21 DR. SUAREZ-ALMAZOR: Good morning. Maria
22 Suarez-Almazor, I'm a professor of medicine at the

1 University of Texas, MD Anderson Cancer Center.
2 DR. HOPKINS: Good morning. Karen Hopkins,
3 associate professor at NYU School of Medicine in
4 developmental behavioral pediatrics.
5 DR. CRAWFORD: Good morning. My name is
6 Stephanie Crawford. I'm associate professor and
7 associate head of the department of pharmacy
8 administration at the University of Illinois. And
9 as a Chicagoan, I'm very happy for the polite,
10 little amount of snow outside.
11 MR. YESENKO: I'm Michael Yesenko, the
12 patient representative, and I'm from Maryland.
13 DR. MCNICHOLAS: Good morning. I'm Laurie
14 McNicholas from the University of Pennsylvania.
15 I'm a psychiatrist.
16 DR. SMITH: Good morning. I'm Bob Smith.
17 I'm a practicing podiatrist, pharmacist, and I'm
18 the assistant clinical professor at Western
19 University.
20 MS. GRAVOIS: Good morning. Angie Gravois,
21 patient representative.
22 DR. OLBRISCH: Mary Ellen Olbrisch. I'm a

1 clinical health psychologist, professor of
2 psychiatry and surgery at Virginia Commonwealth
3 University.
4 DR. LORENZ: Good morning. I'm Karl Lorenz
5 from Los Angeles, California. I am a practicing
6 primary care physician as well as a palliative
7 medicine physician, and I conduct health services
8 research for the Department of Veterans Affairs.
9 I'm a faculty member at UCLA and RAND Health.
10 DR. MENDELSON: And I'm John Mendelson. I'm
11 a senior scientist at the California Pacific
12 Medical Center Research Institute, big name in San
13 Francisco, and also, professor at UCSF. I do
14 opioid pharmacology research as well as a
15 practicing internist. I try to get them before the
16 palliative care. I try to prevent that.
17 MS. MOORE: Good morning. I'm Melinda
18 Moore. I work in Houston, Texas in interventional
19 pain medicine as a physician assistant.
20 DR. VEGA: My name is Jose Vega. I'm the
21 industry representative, and I'm from global safety
22 at Amgen in Thousand Oaks, California.

1 DR. J. WOODS: Thank you all.
2 For topics such as those being discussed at
3 today's meeting, there are often a variety of
4 opinions, some of which are quite strongly held.
5 Our goal at this meeting would be to have a fair
6 and open forum for discussion of these issues and
7 that individuals can express their views without
8 interruption. Thus as a general reminder,
9 individuals will be allowed to speak into the
10 record only if recognized by me. We look forward
11 to a productive meeting.
12 In the spirit of the Federal Advisory
13 Committee Act and the Government in the Sunshine
14 Act, we ask that the advisory committee members
15 take care that their conversations about the topic
16 at hand take place in the open forum of the
17 meeting.
18 We are aware that members of the media are
19 anxious to speak with the FDA about these
20 proceedings. However, FDA will refrain from
21 discussing the details of the meeting with the
22 media until its conclusion. Also, the committee is

1 reminded to please refrain from discussing the
2 topic during breaks or lunch. Thank you.
3 Commander Kristina Toliver will read the
4 Conflict of Interest Statement.
5 **Conflict of Interest Statement**
6 CMDR TOLIVER: The Food and Drug
7 Administration is convening today's meeting of the
8 Drug Safety and Risk Management Advisory Committee
9 under the authority of the Federal Advisory
10 Committee Act of 1972. With the exception of the
11 industry representative, all members and temporary
12 voting members of the committee are special
13 government employees or regular federal employees
14 from other agencies and are subject to federal
15 conflict of interest laws and regulations.
16 The following information on the status of
17 this committee's compliance with the federal ethics
18 and conflict of interest laws, covered by but not
19 limited to those found at 18 U.S.C. Section 208 of
20 the Federal Food, Drug and Cosmetic Act, is being
21 provided to participants in today's meeting and to
22 the public.

1 FDA has determined that members and
2 temporary voting members of this committee are in
3 compliance with federal ethics and conflict of
4 interest laws. Under 18 U.S.C. Section 208,
5 Congress has authorized FDA to grant waivers to
6 special government employees and regular federal
7 employees who have potential financial conflicts
8 when it is determined that the agency's need for a
9 particular individual's services outweighs his or
10 her potential financial conflict of interest.
11 Related to the discussions of today's
12 meeting, members and temporary voting members of
13 this committee have been screened for potential
14 financial conflicts of interest of their own as
15 well as those imputed to them, including those of
16 their spouses or minor children, and for purposes
17 of 18 U.S.C. Section 208, their employers. These
18 interests may include investments, consulting,
19 expert witness testimony, contracts, grants,
20 CRADAs, teaching, speaking, writing, patents and
21 royalties and primary employment.
22 Today's agenda involves the discussion of

1 the public health benefits and risks, including the
2 potential for abuse of drugs containing
3 hydrocodone, either combined with other analgesics
4 or as an antitussive.
5 The Department of Health and Human Services
6 received a request from the Drug Enforcement
7 Administration for a scientific and medical
8 evaluation and scheduling recommendation for these
9 products in response to continued reports of
10 misuse, abuse, and addiction related to these
11 products. The committee will also discuss the
12 impact of rescheduling these hydrocodone products
13 from Schedule III to Schedule II. This is a
14 particular matters meeting during which general
15 issues will be discussed.
16 Based on the agenda for today's meeting and
17 all financial interests reported by the committee
18 members and temporary voting members, no conflict
19 of interest waivers have been issued in connection
20 with this session.
21 To ensure transparency, we encourage all
22 standing committee members and temporary voting

1 members to disclose any public statements that they
2 have made concerning the topic at issue.
3 With respect to FDA's invited industry
4 representative, we would like to disclose that
5 Dr. Jose Vega is participating in this meeting as a
6 nonvoting industry representative acting on behalf
7 of regulated industry. Dr. Vega's role at this
8 meeting is to represent industry in general and not
9 any particular company. Dr. Vega is employed by
10 Amgen.
11 With regard to FDA's guest speakers, the
12 agency has determined that the information to be
13 provided by these speakers is essential. The
14 following interests are being made public to allow
15 the audience to objectively evaluate any
16 presentation and/or comments made by the speakers.
17 Dr. Kevin Zacharoff has acknowledged that
18 his employer, Inflexxion, has received unrestricted
19 educational grants from Actavis and Endo
20 Pharmaceuticals.
21 Dr. Lavonas would like to disclose that he
22 is the associate director of the Rocky Mountain

1 Poison and Drug Center, a department of the Denver
2 Health and Hospital Authority. The Rocky Mountain
3 Poison and Drug Center operates the Researched
4 Abuse, Diversion and Addiction-Related
5 Surveillance, RADARS, system. The RADARS system is
6 funded by subscription fees by industry and
7 operates under the director of an independent
8 scientific advisory board.
9 In the past 12 months, Dr. Lavonas served as
10 a principal investigator on five research projects,
11 involving opioid medication safety funded by grants
12 or contracts from industry, which involved RADARS
13 systems opioids, oxymorphone or buprenorphine.
14 Dr. Lavonas did not receive personal remuneration
15 or salary support from these interests.
16 As guest speakers, Drs. Lavonas and
17 Zacharoff will not participate in committee
18 deliberations, nor will they vote.
19 In addition, Drs. Edward Michna and Sharon
20 Walsh are special government employees attending
21 this meeting as presenters.
22 We would like to remind members and

1 temporary voting members that if the discussions
2 involve any other products or firms not already on
3 the agenda for which an FDA participant has a
4 personal or imputed financial interest, the
5 participants need to exclude themselves from such
6 involvement, and their exclusion will be noted for
7 the record.
8 FDA encourages all other participants to
9 advise the committee of any financial relationships
10 that they may have with the firms that make
11 hydrocodone-containing products. Thank you.
12 DR. J. WOODS: We will now proceed with the
13 FDA opening remarks from Dr. Michael Klein,
14 Michael.
15 Michael, excuse me, I want to interrupt you
16 before you even get started. There are some people
17 who came in just now. Would you please introduce
18 yourselves?
19 DR. JONES: Sorry for being late. Chris
20 Jones with the Centers for Disease Control and
21 Prevention; serve as an acting team leader for the
22 prescription drug overdose team in the injury

1 center at CDC.

2 DR. J. WOODS: Thank you.

3 DR. SIMONI-WASTILA: Linda Simoni-Wastila,

4 University of Maryland, Baltimore. I do

5 population-based research in the areas of

6 controlled substances.

7 **Opening Remarks - Michael Klein**

8 DR. KLEIN: Dr. Woods and members of

9 the committee, invited guests, good morning and

10 welcome to this meeting of the Drug Safety and Risk

11 Management Advisory Committee. Today we are

12 discussing the abuse potential of hydrocodone and

13 combination drug products, which are used for

14 treatment of pain and as antitussives.

15 With enactment of the Controlled Substances

16 Act in 1970, these hydrocodone combination drug

17 products were placed legislatively into

18 Schedule III of the Act. This rescheduling issue

19 was originally going to be discussed by the

20 advisory committee on October 29th and 30th, 2012,

21 but had to be postponed because of Hurricane Sandy,

22 which had serious effects on the Washington, D.C.

1 area and had disastrous effects on much of the
2 northeastern United States.
3 At the present time, the agency is in the
4 process of planning several meetings that relate to
5 the regulation and medical use of opioid drug
6 products. This meeting is focused only on the
7 scheduling of the hydrocodone combination products.
8 In 1999, the Drug Enforcement Administration
9 received a petition asking DEA to reschedule the
10 products to Schedule II because of increasing
11 reports of abuse. In following the provisions of
12 the CSA, DEA gathered and reviewed data on abuse
13 and diversion of these drug products. In 2004, DEA
14 notified the assistant secretary for health of the
15 Department of Health and Human Services about the
16 petition and requested a scientific and medical
17 evaluation and scheduling recommendation for the
18 hydrocodone combination drug products.
19 The department responded in 2008 that the
20 scientific and medical evaluation did not support a
21 recommendation for rescheduling the hydrocodone
22 combination products to Schedule II and that the

1 products should remain in Schedule III.
2 DEA's deputy assistant administrator in the
3 Office of Diversion Control sent a response to the
4 Center for Drug Evaluation Research in 2009 and
5 referred to the HHS recommendation and asked for a
6 reanalysis of our data.
7 The responsibility for conducting the
8 scientific and medical evaluation of substances for
9 control under the CSA is delegated from HHS to the
10 Food and Drug Administration, Center for Drug
11 Evaluation and Research. The National Institute on
12 Drug Abuse, NIDA, which is part of the National
13 Institutes of Health, participates with FDA on drug
14 scheduling recommendations.
15 DEA must request a scientific and medical
16 evaluation from the Department of Health and Human
17 Services before adding a drug to or transferring a
18 drug between the schedules. The HHS evaluation is
19 binding on the DEA as scientific and medical
20 matters.
21 The level of CSA scheduling determines the
22 regulations and penalties that will apply to the

1 products. The advice we are seeking from this
2 committee is whether the products should remain on
3 Schedule III or be rescheduled to Schedule II. As
4 such, the differences in the regulations for
5 Schedule III and Schedule II drugs will be
6 discussed.
7 Importantly, related issues are how
8 rescheduling might impact the availability of
9 medications to patients and appropriate use of the
10 drug, including healthcare delivery as well as
11 reducing abuse. And these will all be addressed.
12 The FDA presentation will include a
13 discussion of the statutory and regulatory issues
14 and drug scheduling as well as the results of
15 analyses by several offices in the Center for Drug
16 Evaluation and Research. These include an analysis
17 of issues related to the pharmacology and abuse
18 potential and medical utilization of hydrocodone
19 from the CDER controlled substance staff and an
20 analysis of the epidemiology of use and abuse of
21 hydrocodone by the Office of Surveillance and
22 Epidemiology.

1 The FDA background materials include
2 information on the potential impact that tighter
3 controls on hydrocodone would have on the
4 availability and use to treat pain.
5 Other presentations will discuss the abuse
6 potential assessments of the products in human
7 studies -- and this will be presented by Dr. Walsh
8 from the University of Kentucky -- as well as the
9 medical use of the hydrocodone combination products
10 by Dr. Michna from Brigham and Women's Hospital and
11 a presentation by the DEA.
12 These will be followed by presentations on
13 physician education by Dr. Zacharoff and
14 prescription drug monitoring programs by
15 Dr. Lavonas, both areas intended to contribute to
16 reducing abuse of opioids.
17 Various professional organizations will
18 discuss hydrocodone combination product use and
19 abuse in medical treatment and the rescheduling.
20 This includes representatives from the Generic
21 Pharmaceutical Association, which is representing
22 some drug product sponsors; the American

1 Pharmacists Association; the American Dental
2 Association; the American Association of Oral and
3 Maxillofacial Surgeons; the American Optometric
4 Association; the American Association of Pain
5 Medicine; and the American Society of Addiction
6 Medicine.
7 On day 2 of the meeting, we will hold an
8 open public hearing so the public can have the
9 opportunity to provide their comments on the
10 important issues being discussed at this advisory
11 committee.
12 Through this advisory committee, we are
13 today seeking your advice on the abuse potential of
14 hydrocodone combination products. You will be
15 asked to discuss the following: What the
16 pharmacology data and the epidemiology data
17 suggests about the potential for abuse of
18 hydrocodone combination products compared with
19 drugs that are currently in Schedule II.
20 You will also be asked to discuss the impact
21 that rescheduling of hydrocodone combination
22 products from Schedule III to II of the Controlled

1 Substances Act would have on prescribing patterns
2 for these products and other opioids as well,
3 including delivery of healthcare in the United
4 States; including impacts on distribution,
5 manufacturing, and pharmacies; availability of
6 these products for patients with appropriate needs,
7 as well as by individuals seeking to abuse opioids;
8 also, considerations of other activities that could
9 contribute to reducing abuse and misuse of the
10 hydrocodone combination products.
11 And finally, based on the background
12 materials, presentations and discussions, you will
13 be asked for your recommendation on whether the
14 hydrocodone combination products should be
15 rescheduled from Schedule III to Schedule II of the
16 Controlled Substances Act. And you will be asked
17 to please explain the basis for your vote.
18 We consider this advisory committee to be an
19 important opportunity to hear from experts and the
20 public on how to seek a balance between appropriate
21 availability of these important pain medications to
22 patients and necessary controls to deter misuse and

1 abuse.
2 The advisory committee of outside experts
3 will provide FDA with an important opinion and
4 recommendation about whether the hydrocodone
5 combination products should be rescheduled to
6 Schedule II of the Controlled Substances Act.
7 FDA has not yet made any final conclusions
8 about the issues discussed at this meeting, and
9 your advice will inform FDA's ultimate
10 recommendation to the assistant secretary for
11 health of the Department of Health and Human
12 Services.
13 We thank you in advance for participating in
14 this meeting and providing us with your expertise
15 and insights on this important public health issue.
16 DR. J. WOODS: Thank you, Michael, for that
17 nice introduction. I think we'll go now to the
18 individual FDA speakers, and we'll recognize them
19 as they come to the podium. The snowman delivered
20 one last member of the committee, and I'll ask her
21 to introduce herself.
22 MS. MAY: My name is Rosemary May. I'm a

1 nurse practitioner at the National Institutes of
2 Health with NHLBI.
3 DR. J. WOODS: Thank you. And now may we
4 proceed with the FDA presentations?
5 **FDA Presentation - Julie Finegan**
6 MS. FINEGAN: Good morning. My name is
7 Julie Finegan. I'm an attorney with the Office of
8 the Chief Counsel of the Food and Drug
9 Administration, and I'm here to provide a brief
10 overview of the Controlled Substances Act and the
11 scheduling process.
12 The Controlled Substances Act was first
13 enacted in 1970 to regulate the manufacture,
14 importation, possession, use and distribution of
15 certain substances. While DEA is primarily
16 responsible for interpreting and enforcing the
17 Controlled Substances Act, the Department of Health
18 and Human Services, or HHS, has a number of
19 responsibilities, several of which are performed on
20 behalf of HHS by FDA.
21 One of the functions that FDA performs for
22 the Department of Health and Human Services under

1 the Controlled Substances Act is preparing a
2 scheduling recommendation for the Department of
3 Health and Human Services. And FDA completes a
4 medical and scientific evaluation and scheduling
5 recommendation for the department with the
6 concurrence of the National Institute on Drug
7 Abuse.
8 The HHS scheduling recommendation is binding
9 on DEA as to scientific and medical matters, and
10 DEA cannot schedule a substance if the Department
11 of Health and Human Services recommends that it not
12 be controlled. Once HHS has transferred to DEA a
13 scheduling recommendation, DEA goes through a
14 rulemaking process to schedule the drug.
15 Under the Controlled Substances Act, there
16 are five schedules. Schedule I is the most
17 restrictive. Substances in Schedule I do not have
18 an accepted medical use in treatment in the United
19 States. Drugs that have abuse potential but have a
20 currently accepted medical use in treatment in the
21 United States, for example, FDA approval are
22 controlled in Schedules II through V of the

1 Controlled Substances Act.
2 A substance's schedule dictates the
3 requirements regarding physical security, quotas,
4 prescribing, and registration requirements.
5 Section 202 of the Controlled Substances Act, and
6 the Drug Enforcement Administration regulations at
7 21 CFR Part 1308, lists the drugs and substances
8 that are controlled in each of the five schedules.
9 When FDA prepares a scheduling
10 recommendation, it considers eight factors that are
11 spelled out in the Controlled Substances Act. And
12 I'm going to describe each of the eight factors
13 over the next two slides.
14 In preparing a scheduling recommendation,
15 FDA considers the scientific evidence of the drug's
16 pharmacological effect, if known; the state of
17 current scientific knowledge regarding the drug or
18 substance; the risk, if any, to the public health;
19 the drug's psychic or physiological dependence
20 liability; and whether the substance is an
21 immediate precursor of a substance already
22 controlled.

1 FDA also considers the scientific and
2 medical considerations involved in the following
3 three factors: the drug's actual or relative
4 potential for abuse, the drug's history and current
5 pattern of abuse, and the scope, duration and
6 significance of abuse.
7 The actual relative or potential for abuse
8 is not defined in the Controlled Substances Act.
9 However, there is information in the legislative
10 history, which is helpful in considering that
11 factor. In determining a drug's actual or relative
12 potential for abuse, FDA will consider whether
13 individuals are taking the substance in amounts
14 sufficient to create a hazard to their health; the
15 safety of others or to the community; whether there
16 is sufficient diversion of the drug from legitimate
17 drug channels; whether individuals are taking the
18 substance on their own initiative rather than on
19 the basis of medical advice from a licensed
20 practitioner; and whether the drug is related in
21 its action to a substance already listed as having
22 a potential for abuse such that it is likely that

1 the drug would have the same potential for abuse as
2 the drug already listed; or that it is reasonable
3 to assume that there may be sufficient diversions
4 used contrary to or without medical advice; or a
5 substantial capacity of creating a hazard to the
6 health of the user or to the safety of the
7 community.
8 After considering the eight factors I just
9 described, HHS must make a recommendation as to the
10 appropriate schedule. Each schedule has three
11 findings that must be made under the Controlled
12 Substances Act, and these findings for each
13 schedule are set out in Section 202 of the Act.
14 For Schedule I, three findings require that
15 FDA find that the drug have a high potential for
16 abuse, that the drug have no currently accepted
17 medical use in treatment in the United States, and
18 that the drug lacks accepted safety for use under
19 medical supervision.
20 For Schedule II, FDA must find that the drug
21 have a high potential for abuse, that the drug have
22 a currently accepted medical use in treatment in

1 the United States, or a currently accepted medical
2 use with severe restrictions. And the third
3 finding is that abuse of the substance may lead to
4 severe psychological or physical dependence.
5 Placement of the drug in Schedules III, IV
6 and V all require that the drug have a currently
7 accepted medical use in treatment in the United
8 States. Schedule III requires a finding that the
9 drug's potential for abuse is less than that of
10 drugs or substances in Schedules I or II and that
11 abuse of the substance may lead to moderate or low
12 physical dependence or high psychological
13 dependence.
14 Placement of the drug in Schedule IV
15 requires that the drug have a low potential for
16 abuse relative to drugs in Schedule III and that
17 abuse of the substance may lead to limited physical
18 dependence or psychological dependence relative to
19 substances in Schedule III.
20 And finally, Schedule V requires a finding
21 that the drug have a low potential for abuse
22 relative to substances in Schedule IV and that

1 abuse of the substance may lead to limited physical
2 dependence or psychological dependence relative to
3 substances in Schedule IV.
4 With regard to hydrocodone specifically, the
5 Controlled Substances Act places hydrocodone
6 substance in Schedule II of the Act. But it places
7 hydrocodone combination products containing limited
8 amounts of hydrocodone combined with other active
9 ingredients in Schedule III of the Controlled
10 Substances Act.
11 The schedule in which a drug is placed
12 affects the regulatory requirements with regard to
13 registration, recordkeeping, dispensing limits,
14 security, quotas and prescribing. And we're going
15 to talk about a few of those on the next couple of
16 slides.
17 A couple of the key differences between the
18 Schedule II and Schedule III regulations, one of
19 the significant ones is security. Schedule II
20 drugs require -- have very specific -- the drug
21 enforcement regulations have very specific
22 specifications for storage of Schedule II drugs and

1 for the type of vault in which the drugs must be
2 stored.
3 There are different recordkeeping
4 requirements for distribution and sales of
5 Schedule II substances. Schedule II substances
6 also require a written prescription with limited
7 exceptions for emergency prescribing and no
8 refills. However, a doctor can prescribe up to
9 three prescriptions for a maximum of a 90-day
10 supply for a Schedule II substance. For Schedule
11 III substances, a doctor can provide either a
12 written or oral prescription, and the prescription
13 can allow for up to five refills in six months.
14 The factual background with regard to the
15 scheduling of hydrocodone combination products, in
16 2004, DEA transmitted to the Department of Health
17 and Human Services a request that HHS prepare the
18 scientific and medical evaluation and scheduling
19 recommendation for hydrocodone combination
20 products. In 2008, HHS transmitted to DEA a
21 recommendation to maintain hydrocodone combination
22 products in Schedule III of the Controlled

1 Substances Act. And in 2009, FDA submitted new
2 data to HHS and requested a reevaluation of our
3 2008 recommendation.
4 In 2012, FDA announced a public advisory
5 committee meeting to consider the public health
6 benefits and risks, including the potential for
7 abuse, of drugs containing hydrocodone combined
8 with other analgesics or as an antitussive.
9 On July 9th, 2012, President Obama signed
10 into law the Food Drug Administration Safety and
11 Innovation Act. Section 1139 of FDASIA is titled
12 Scheduling of Hydrocodone, and this section of
13 FDASIA requires FDA to hold a public meeting to
14 solicit advice and recommendations to assist in
15 conducting a scientific and medical evaluation and
16 scheduling recommendation to DEA regarding drug
17 products containing hydrocodone combined with other
18 analgesics or as an antitussive.
19 Section 1139 requires that FDA solicit input
20 from a variety of stakeholders, including patients,
21 healthcare providers, harm prevention experts,
22 NIDA, CDC and DEA regarding the health benefits and

1 risks, including the potential for abuse and the
2 impact of rescheduling these hydrocodone
3 combination products from Schedule III to Schedule
4 II. FDASIA also requires that FDA post a
5 transcript of this meeting on its website.
6 In summary, key reminders of why we're here
7 today is a decision as to whether hydrocodone
8 should remain in Schedule III of the Controlled
9 Substances Act or be moved to Schedule II of the
10 Act. And so again, the findings that FDA must make
11 to place hydrocodone products in each of these
12 schedules are listed on this last slide.
13 Schedule III requires that FDA make a
14 finding that the hydrocodone products have a high
15 potential for abuse, that they have a currently
16 accepted medical use in treatment in the United
17 States or a currently accepted medical use with
18 severe restrictions, and a finding that abuse of
19 the substance may lead to severe psychological or
20 physical dependence.
21 Placement in Schedule III requires that the
22 drug have a potential for abuse less than drugs or

1 substances in Schedules I or II, that the drug have
2 a currently accepted medical use in treatment in
3 the United States, and that abuse of the drug may
4 lead to moderate or low physical dependence or high
5 psychological dependence.
6 DR. J. WOODS: I'm going to ask Dr. Calderon
7 to take the podium now, and then we'll have
8 clarifying questions from the committee of the FDA
9 presentations.
10 Dr. Calderon, hold on just a moment. There
11 was another snowman just delivered to the
12 committee.
13 Could you introduce yourself, please?
14 DR. DENISCO: Yes. I'm Richard Denisco,
15 medical officer at National Institute of Drug
16 Abuse.
17 DR. J. WOODS: Thank you.
18 Dr. Calderon.
19 **FDA Presentation - Silvia Calderon**
20 DR. CALDERON: Good morning. My name is
21 Sylvia Calderon. I am a team leader pharmacologist
22 in the controlled substance staff within the Center

1 for Drug Evaluation and Research. In my
2 presentation, I will be covering the schedule
3 status of hydrocodone combination products and
4 describe -- I will discuss the schedule status of
5 hydrocodone combination products and currently
6 available products. I will briefly describe the
7 roles of the Drug Enforcement Administration and
8 the Food and Drug Administration in the
9 rescheduling petition, briefly mention the
10 highlights of the 2008 Department of Health and
11 Human Services, HHS, recommendation and the 2009
12 DEA analysis and request for reevaluation of the
13 data provided in 2008 by HHS.
14 I will present an overview of the controlled
15 substance staff analysis on the abuse of
16 hydrocodone as well as an overview of the CDER
17 Office of Surveillance and Epidemiology drug
18 availability and epidemiological analysis. Lastly,
19 I will summarize and point out some areas for you
20 to consider.
21 One of the first questions to answer is what
22 is the schedule status of hydrocodone substance and

1 combination products. At the time of the enactment
2 of the Controlled Substances Act, Congress placed
3 hydrocodone in two schedules. Hydrocodone
4 substance was placed in Schedule II of the
5 Controlled Substances Act. Thus, hydrocodone
6 substance is subject to all the controls imposed by
7 these schedules, including manufacturing quotas,
8 which are yearly established by the DEA. Also, we
9 don't have any single product containing
10 hydrocodone currently on the market.
11 Hydrocodone in specified amounts and in
12 combination with specified amounts of isoquinoline
13 alkaloids or one or more therapeutically active
14 non-narcotic ingredient was placed in Schedule III.
15 Currently, we do not have any combination product
16 with isoquinoline alkaloids.
17 Currently, hydrocodone combination products
18 in Schedule III are those that contain no more than
19 300 milligrams of dihydrocodeinone -- and this is
20 another name for hydrocodone -- per 100 milliliters
21 or not more than 15 milligrams of hydrocodone
22 measured as the free base per dosage unit with one

1 or more active non-narcotic ingredients in
2 recognized amounts.
3 What are the combination products currently
4 approved and made available on the market?
5 Hydrocodone is present in products used as
6 analgesics and as cough suppressants. Currently on
7 the market, there are 81 analgesic products
8 approved containing up to 10 milligrams of
9 hydrocodone bitartrate per dosage unit and
10 acetaminophen or ibuprofen as the non-narcotic
11 component. All these products but one are generic
12 products. Also, these products are all available
13 as immediate release formulations.
14 There are 12 cough suppressant products
15 approved containing also up to 10 milligrams of
16 hydrocodone bitartrate per dosage unit, and usually
17 they are combined with chlorpheniramine,
18 homatropine, or pseudoephedrine. All products but
19 three are generic products. These products are
20 available in both immediate and extended release
21 formulations.
22 Now, I will briefly describe the roles of

1 the DEA and FDA on the rescheduling petition of
2 hydrocodone combination products.
3 In 1999, the DEA received a request from a
4 citizen to reschedule hydrocodone combination
5 products to Schedule II of the CSA. DEA after
6 gathering information, compiling information,
7 accepting that petition, put together an eight-
8 factor analysis, and in 2004, DEA submitted that
9 eight-factor analysis to the Department of Health
10 and Human Services for a medical and scientific
11 evaluation.
12 Within HHS, the function of providing a
13 scientific and medical evaluation is delegated to
14 the FDA. Within FDA, that function is delegated to
15 the Center for Drug Evaluation and Research.
16 Within CDER, it is the controlled substance staff
17 that takes the lead in completing the evaluation
18 and making recommendations for scheduling.
19 Upon receiving the initial DEA request in
20 2004, CSS began to collect information to respond
21 to the petition, and CSS requested the assistance
22 of the Division of Anesthesia, Analgesia, and

1 Addiction Products and of the Division of
2 Epidemiology within the Office of Surveillance and
3 Epidemiology to address the epidemiology and
4 medical aspects of the review.
5 Once the evaluation was completed and with
6 the concurrence of the National Institute of Drug
7 Abuse and the FDA office of chief counsel, the FDA
8 commissioner submitted the recommendation to the
9 assistant secretary for health.
10 On March 2008, the assistant secretary for
11 health concurred with FDA's findings and forwarded
12 the recommendation to the deputy administrator of
13 the DEA. This recommendation was entitled Basis
14 for Recommendation to Maintain Hydrocodone
15 Combination Products in Schedule III of the
16 Controlled Substances Act.
17 In response to the 2008 recommendation, in
18 2009, DEA submitted an analysis with updated data
19 and requested CDER to reevaluate the 2008
20 recommendation. This 2009 request once again
21 engaged the whole CDER team, gathering new data and
22 reviewing the data submitted by the DEA. And in

1 the next slides, I will present an overview of the
2 DEA findings followed by an overview of the
3 findings of the CDER review team.
4 As I mentioned in the prior slide, in 2008,
5 the ASH, representing HHS, recommended to the DEA
6 to maintain hydrocodone combination products in
7 Schedule III of the Controlled Substances Act.
8 This recommendation was based upon the following
9 three findings: Hydrocodone combination products,
10 meaning those products in combination with other
11 non-narcotic ingredients, have a lower potential
12 for abuse than drugs or other substances in
13 Schedule II -- we'll remind you that already
14 hydrocodone substance is in the Schedule II of the
15 Controlled Substance Act -- currently accepted
16 medical use in the treatment of the U.S., and abuse
17 of the hydrocodone combination products may lead to
18 moderate or low physical dependence or high
19 psychological dependence.
20 In 2009, the DEA submitted an analysis with
21 updated data and requested that CDER reevaluate the
22 2008 recommendation. DEA analysis and request for

1 evaluation focused primarily on the following
2 areas: abuse potential of hydrocodone,
3 availability of hydrocodone combination products,
4 epidemiological analysis of actual indicators of
5 abuse in the 2008 recommendation.
6 In the next slides, I will briefly describe
7 the DEA's position in each of these three areas,
8 and I will present an overview of the CDER
9 findings. Regarding the abuse potential of
10 hydrocodone combination products, DEA states that
11 hydrocodone substance and in combination produce
12 similar abuse-related effects to other Schedule II
13 opioids such as morphine, oxycodone, and
14 hydromorphone, based on the review of human abuse
15 potential studies cited in the 2008 recommendation.
16 In response to the DEA request, CSS reviewed
17 six studies published from 2003 to date and
18 concluded that hydrocodone single entity and in
19 combination produced similar effects to those of
20 typical Schedule II opioids such as morphine and
21 hydromorphone.
22 Human abuse potential studies provide

1 information on the relative abuse potential of a
2 drug in humans and contribute to the assessment of
3 the likelihood of abuse of a drug when introduced
4 to the market. These studies do not capture and do
5 not measure other variables that may impact the
6 abuse of a product once on the market. For
7 example, these studies cannot measure the effect of
8 drug availability, availability of other drugs of
9 abuse, and the effects of street drug prices on
10 abuse choices.
11 CSS review showed that hydrocodone single
12 entity and hydrocodone in combination with other
13 non-narcotic substances produced similar effects to
14 those of typical mu agonists, such as morphine,
15 oxycodone, hydromorphone, all Schedule II, but
16 produce these effects in a dose-related manner.
17 These effects include liking, high, and depending
18 on the study population and product administered,
19 some of these studies detected unpleasant effects,
20 and hydrocodone produces effects such as dizziness
21 and increased rate of nausea.
22 Though I do recognize that there are several

1 methodological variables with these studies that
2 may have impacted the outcomes and the
3 interpretation of the data, these studies show that
4 hydrocodone single entity and in combination
5 produce effects such as high and liking at doses of
6 hydrocodone bitartrate equal or greater than 15
7 milligrams when taken orally. I should also point
8 out that currently the highest strength of
9 hydrocodone combination products is 10 milligrams
10 of hydrocodone bitartrate, and also, some of the
11 strength and formulations using some of the
12 described studies use products that are not
13 currently available on the market.
14 These studies will be further discussed in
15 more detail by Dr. Sharon Walsh.
16 Now, going back to the 2009 DEA analysis and
17 request for reevaluation, on the availability of
18 hydrocodone in combination products, DEA states
19 that the diversion, trafficking, and abuse of
20 hydrocodone and oxycodone are mainly associated
21 with pharmaceutical products manufactured,
22 distributed and prescribed within the United

1 States. There is no clandestine production of
2 these substances. The production and prescription
3 of these products have increased dramatically in
4 the recent years.
5 It is unquestionable that abuse, diversion
6 and trafficking of the Schedule II oxycodone and
7 Schedule III hydrocodone combination products
8 exists. And it's unquestionable that these opioids
9 are widely prescribed because of their role in the
10 management of pain. However, how do we measure the
11 effect of available drug for abuse?
12 As I mentioned before, clinical abuse
13 liability studies are predictive of the abuse
14 potential, but these studies do not evaluate other
15 real-world factors such as amount of drug available
16 for abuse on the street, competitive availability
17 of other opioids, or street prices. So one way to
18 measure the effect of availability on abuse is
19 measuring the consequences of abuse relative to the
20 amount of drug available for abuse. This approach
21 will be discussed later in the Office of
22 Epidemiology presentations.

1 What do we know about the availability of
2 hydrocodone combination analgesics? OSE at the FDA
3 analysis show that in 2011, approximately 131
4 million prescriptions for hydrocodone combination
5 analgesics were prescribed whereas 34.6 million
6 prescriptions for oxycodone combination products
7 were dispensed. Forty-seven million patients
8 received hydrocodone combination products, and
9 approximately 15 million patients received
10 oxycodone combination products.
11 These high volume of prescriptions is an
12 indication of the major role these products play in
13 the management of pain. Prescribing patterns,
14 including prescriber specialties, indication for
15 use, and length of treatment for hydrocodone and
16 oxycodone products, will be presented in further
17 detail by Dr. Gill from the Office of Surveillance
18 and Epidemiology.
19 Going back to the 2009 DEA analysis of the
20 epidemiological data and request for reevaluation,
21 DEA measured levels of abuse using abuse ratios.
22 Abuse ratios measure the occurrence of an abuse-

1 related event that we call numerator per amount of
2 drug available for abuse, we see that as
3 denominator, relative to other drugs with similar
4 pharmacology and medical use, that they are called
5 comparator products or drugs.
6 DEA calculated abuse ratios using different
7 denominators from those submitted in the 2008 HHS
8 recommendation, and DEA also used oxycodone
9 products as the only comparator drug. Based on the
10 calculated ratios, DEA concluded that the
11 non-narcotic active ingredients present in
12 hydrocodone combination products do not reduce the
13 abuse potential of hydrocodone.
14 In response, the Office of Surveillance and
15 Epidemiology at CDER evaluated the data submitted
16 by DEA. In agreement with the DEA, OSE also used
17 oxycodone-containing products for comparison
18 purposes. Also, OSE calculated abuse ratios and
19 extensively researched the pros and cons of the use
20 of various numerators and denominators.
21 The selection of the appropriate comparator
22 and the appropriate numerator and denominator is

1 critical. Why? Because abuse potential is a
2 relative measure. It's a relative measure to that
3 of other drugs with known abuse potential. In
4 addition, OSE will further discuss the
5 epidemiological analysis in the following
6 presentations.
7 After the evaluation of the limitations of
8 several numerators and denominators, OSE identified
9 the number of abuse-related emergency department,
10 ED, visits in the Drug Abuse Warning Network, DAWN,
11 as the numerator that best captures abuse-related
12 events for specific drug products, meaning for
13 hydrocodone combination products versus oxycodone
14 single entity, oxycodone single entity immediate
15 and extended release and oxycodone combination
16 products. This numerator has the granularity to
17 provide that information.
18 In addition, the total number of dispensed
19 units, tablets or capsules, OSE identified this
20 denominator as the one that likely provides the
21 best metric of units available for abuse.
22 Using this numerator and denominator, OSE

1 analysis show that hydrocodone combination products
2 are widely abused, that abuse ratios for
3 hydrocodone combination analgesic products are
4 lower than the abuse ratios for oxycodone-
5 containing products. And by comparison of the
6 abuse ratios for oxycodone single entity, and for
7 the opioid analgesic tramadol single entity to the
8 abuse ratios for the same opioids in combination
9 with acetaminophen, a non-narcotic analgesic, OSE
10 concluded that the addition of a non-narcotic
11 ingredient reduces the levels of abuse of these
12 opioid analgesics.
13 Thus, it can be inferred that higher abuse
14 ratios would be likely observed for a hypothetical
15 hydrocodone single-entity product when compared to
16 the analgesic combination products. And in this
17 way, indirectly demonstrating that the addition of
18 a non-narcotic ingredient, in fact, reduces the
19 abuse potential of hydrocodone.
20 Dr. Dormitzer will discuss these data in
21 more detail.
22 In summary, after reevaluating the data

1 submitted by the DEA in 2009, we can certainly
2 agree that there is not a single test or analysis
3 that can provide a full characterization of the
4 abuse potential of the drug. We also could agree
5 that there are several factors that need to be
6 evaluated when assessing the relative abuse
7 potential of any drug. These factors, the
8 pharmacology, as well as the abuse-related effects,
9 the medical use, which is highly correlated with
10 the availability of the drug, as well as the levels
11 of abuse and consequences of abuse, all these
12 factors need to be considered.
13 Hydrocodone combination products fulfill an
14 important role in the management of pain as
15 evidenced by the number of prescriptions dispensed
16 yearly and the number of patients being prescribed
17 these products. Other points for your
18 consideration, the consequences of rescheduled
19 hydrocodone combination products on patients'
20 access and proper management of pain needs to be
21 considered. Also, alternatives to rescheduling
22 these products such as educational efforts and the

1 use of prescription monitoring programs need to be
2 considered and evaluated because they may provide
3 an effective way of reducing the levels of abuse of
4 hydrocodone combination products.
5 Thank you very much for your attention.
6 DR. J. WOODS: Thank you. Dr. Calderon.
7 We'll leave clarifying questions till later.
8 Our next speaker is Dr. Gill, I think.
9 **FDA Presentation - Rajdeep Gill**
10 DR. GILL: Good morning. My name is Rajdeep
11 Gill, and I'm a drug utilization analyst in the
12 Division of Epidemiology, Office of Surveillance
13 and Epidemiology. Today I will be presenting drug
14 utilization patterns for combination hydrocodone-
15 containing products and selected opioid analgesics
16 in the U.S. from year 2007 through year 2011.
17 My presentation will be in the following
18 order. First, I will present the sales
19 distribution analysis. Then I will present the
20 dispensed prescription and patient level analysis.
21 Following that, I will present prescriber
22 specialty, duration of use, and diagnoses data.

1 Finally, I will present the limitations of my
2 analysis and conclude with a summary of my
3 presentation.
4 Now, I will present the sales data. The IMS
5 Health, IMS National Sales Perspectives database
6 was used to obtain the sales of selected opioids
7 included in this analysis. This database measures
8 the volume of products in units and dollars moving
9 from the manufacturers to retail and non-retail
10 channels of distribution.
11 This graph represents the total weight in
12 kilograms sold for combination hydrocodone-
13 containing analgesics and selected opioid
14 analgesics as comparators, including combination
15 oxycodone-containing analgesics, oxycodone
16 immediate release, oxycodone extended release,
17 morphine extended release, morphine immediate
18 release and hydromorphone. Approximately 64,000
19 kilograms of combination hydrocodone-containing
20 analgesics were sold in year 2011, an increase from
21 approximately 50,000 kilograms sold in year 2007.
22 The sales of combination hydrocodone-

1 containing analgesics far exceeds the sales of any
2 other individual opioid analgesic selected in this
3 analysis. As displayed in this chart, 66 percent
4 of combination hydrocodone-containing analgesics
5 were distributed from the manufacturer to retail
6 settings, 28 percent to non-retail pharmacies, and
7 7 percent to mail order. Therefore, the drug
8 utilization analysis in my presentation is focused
9 on U.S. outpatient retail pharmacy settings.
10 Next, I will be presenting prescription and
11 patient level data. IMS' Vector One national and
12 total patient tracker were used to analyze U.S.
13 outpatient retail pharmacy utilization patterns.
14 VONA and TPT are national level projected
15 prescription and patient-centric tracking services.
16 They measure dispensing of prescriptions out of
17 retail pharmacies into the hands of consumers.
18 Data are obtained from approximately 59,000
19 pharmacies throughout the U.S., which accounts for
20 nearly all retail pharmacies in the country and
21 nearly half of all retail prescriptions dispensed
22 nationwide. From this database, we can also obtain

1 data on prescribing specialties.
2 This figure shows the estimated number of
3 prescriptions dispensed for combination
4 hydrocodone-containing analgesics and antitussives.
5 The number of combination hydrocodone-containing
6 analgesic prescriptions increased from
7 approximately 121 million prescriptions dispensed
8 during year 2007 to approximately 131 million
9 prescriptions dispensed during year 2011.
10 In contrast, the number of hydrocodone-
11 containing antitussive prescriptions decreased from
12 approximately 12 million prescriptions dispensed
13 during year 2007 to approximately 5 million
14 prescriptions dispensed during year 2011,
15 accounting for more than 50 percent decrease in
16 prescription volume.
17 Throughout the time period examined,
18 combination hydrocodone-containing analgesics
19 accounted for the majority of the prescriptions
20 arranging from 91 to 96 percent of total
21 prescriptions dispensed. Therefore, the drug
22 utilization analysis in my presentation will be

1 focused on combination hydrocodone-containing
2 analgesics.
3 This graph displays the number of
4 prescriptions dispensed to U.S. outpatient retail
5 pharmacies from year 2007 through year 2011 for
6 combination hydrocodone-containing analgesics,
7 combination oxycodone-containing analgesics,
8 oxycodone immediate release, oxycodone extended
9 release, morphine immediate release, extended
10 release, and hydromorphone.
11 Throughout the time period examined,
12 combination hydrocodone-containing analgesics
13 accounted for approximately two-thirds of the total
14 prescriptions dispensed, followed by oxycodone-
15 containing analgesics with approximately one-
16 quarter of the total prescriptions dispensed.
17 During year 2011, approximately 131 million
18 combination hydrocodone-containing analgesic
19 prescriptions were dispensed followed by 35 million
20 combination oxycodone-containing analgesic
21 prescriptions.
22 In general, the number of prescriptions

1 dispensed increased for all of the agents analyzed
2 with the exception of extended release oxycodone,
3 which decreased during the time period examined.
4 The number of combination hydrocodone-containing
5 analgesic prescriptions exceeded the number of
6 prescriptions for any other individual opioid by at
7 least threefold.
8 Similar trends were observed in unique
9 patient data. During year 2011, approximately
10 47 million patients received combination
11 hydrocodone-containing analgesic prescriptions
12 followed by 15 million patients receiving
13 combination oxycodone-containing analgesic
14 prescriptions. The number of patients receiving
15 dispensed prescriptions increased for all of the
16 agents analyzed with the exception of extended
17 release oxycodone in which the number of patients
18 decreased during the time period examined.
19 Similar to the prescription data, the number
20 of unique patients receiving combination
21 hydrocodone-containing analgesic prescriptions
22 exceeded the number of unique patients receiving

1 any other individual opioid by at least threefold.
2 Now, I will be presenting prescriber
3 specialty data. This table provides percentage of
4 prescriptions for each product dispensed by the top
5 prescribing specialties. Each columns sums to
6 100 percent. Over the cumulative time period, from
7 year 2007 to year 2011, general practice, family
8 medicine, doctor of osteopathy, and internal
9 medicine specialists were the top prescribing
10 specialty accounting for approximately 40 percent
11 of the total prescriptions dispensed for
12 combination hydrocodone-containing analgesics.
13 Similarly, this group was the top prescribing
14 specialty accounting for approximately 35 to
15 40 percent of the total prescriptions dispensed for
16 the other analgesics analyzed.
17 Dentists accounted for approximately
18 10 percent of the total combination hydrocodone-
19 containing prescriptions dispensed and
20 approximately for 5 percent of the total
21 combination oxycodone-containing prescriptions
22 dispensed.

1 The number of dispensed prescriptions
2 prescribed by orthopedic surgeons was relatively
3 higher for combination hydrocodone-containing
4 analgesic prescriptions, accounting for 8 percent,
5 and combination oxycodone-containing analgesic
6 prescriptions, accounting for 9 percent as compared
7 to the other opioid analgesics analyzed.
8 In contrast, the number of prescriptions
9 prescribed by anesthesiologists was relatively
10 lower for combination hydrocodone-containing
11 analgesic prescriptions, accounting for 3 percent,
12 and combination oxycodone-containing analgesic
13 prescriptions, accounting for 4 percent as compared
14 to other opioid analgesics.
15 In general, we observed similar prescribing
16 patterns for combination hydrocodone- and
17 oxycodone-containing analgesic prescriptions.
18 These prescribing patterns suggest that combination
19 hydrocodone- and oxycodone-containing analgesics
20 may be used to treat more acute pain conditions
21 treated by primary care practitioners than chronic
22 pain conditions treated by anesthesiologists.

1 But it is worth mentioning that even though
2 combination hydrocodone-containing analgesics may
3 be used more often for acute pain management,
4 smaller percentage of use for chronic conditions
5 translate into a vast number of prescriptions and
6 patients simply because of the widespread use of
7 hydrocodone-containing analgesics.
8 Next, we look at duration of use. This
9 graph shows the average number of days of therapy
10 dispensed per prescription for year 2011. The
11 average days of therapy for both combination
12 hydrocodone- and oxycodone-containing analgesics
13 was approximately 14 days per prescription.
14 Comparatively, the average days of therapy per
15 prescription for extended release formulations was
16 higher with approximately 27 days for oxycodone
17 extended release and approximately 28 days for
18 morphine extended release.
19 These findings also support the idea that
20 combination hydrocodone- and oxycodone-containing
21 analgesics may be used more often to treat acute
22 pain conditions. However, the data are limited

1 because they do not account for the fact that
2 multiple prescriptions can be dispensed to the same
3 patient over time, and thus do not measure actual
4 duration of use at the patient level. The data
5 also rely on the average or mean, which could be
6 easily skewed by outliers.
7 So to address some of these limitations with
8 average days of therapy analysis, we conducted a
9 crude analysis of total days of therapy on a sample
10 of patients. We used Source Healthcare Analytics
11 Prometis Lx database to conduct a crude duration of
12 use analysis. It measures longitudinal product use
13 based on medical and prescription claims from
14 commercial plans, Medicare Part D plans, Medicaid
15 claims and cash prescription claims.
16 In this analysis, the duration of individual
17 patients' prescriptions was added to gather over a
18 two-year time period from January 2010 through
19 December 2011, ignoring gaps in treatment. The
20 range of therapy days for all selected opioid
21 analgesics was similar from two days up to full two
22 years.

1 For combination hydrocodone- and oxycodone-
2 containing analgesics, the mean days of therapy was
3 eight days and six days, respectively, and the mean
4 or average for each was skewed to 45 days and
5 30 days, respectively. The median days of therapy
6 was 19 days for oxycodone immediate release and
7 31 days for oxycodone extended release. This
8 analysis provides additional support to our theory
9 that combination hydrocodone and combination
10 oxycodone-containing analgesics may be used more
11 often to treat acute pain conditions.
12 Next, we analyzed the diagnoses data.
13 Encuity Research Treatment Answers is a monthly
14 survey that monitors disease states and physician
15 intended prescribing habits on a national level.
16 The database contains data from 3,200 prescribers
17 in the panel that report on all patient activity
18 during one typical workday per month, which is then
19 projected nationally.
20 This slide shows the diagnoses most commonly
21 associated with the use of combination hydrocodone-
22 containing analgesics and selected opioids as

1 reported by office-based physician surveys in the
2 U.S. Diagnoses coded to ICD-9 are linked to each
3 drug product mentioned during a patient encounter
4 and then grouped into a diagnostic category
5 collapsed to three-digit ICD-9 codes.
6 The most common diagnoses associated with
7 the use of combination hydrocodone-containing
8 analgesics included diseases of the musculoskeletal
9 system and connective tissue, accounting for
10 25 percent of the total drug use mentions; diseases
11 of the respiratory system, accounting for
12 21 percent of drug use mentions, which includes
13 diagnoses related to chronic tonsillitis and
14 adenoiditis; and fractures, sprains, contusions,
15 injuries, accounting for 19 percent of total drug
16 use mentions.
17 These diagnoses were similar to those
18 associated with the use of combination oxycodone-
19 containing analgesics, yet very different from
20 those associated with the use of oxycodone
21 immediate release and morphine immediate and
22 extended release.

1 The single-ingredient opioid analgesics were
2 mentioned more often in relation to diseases of the
3 musculoskeletal system and connective tissue
4 ranging from 41 to 68 percent of total drug use
5 mentions and with headaches and nerve pain ranging
6 from 15 to 38 percent of total drug use mentions.
7 These data also appear to support the idea
8 that combination hydrocodone- and oxycodone-
9 containing analgesics appear to be used more often
10 to treat acute pain, whereas the single-ingredient
11 opioid analgesics appear to be used more often for
12 the treatment of chronic pain conditions.
13 As we mentioned earlier, even though it
14 appears that combination hydrocodone-containing
15 analgesics are more often used for acute pain
16 conditions, a small percentage of use in chronic
17 pain conditions can translate into a large number
18 of patients using it for chronic pain conditions as
19 well.
20 Before I conclude, I would like to disclose
21 the limitations of this analysis. This analysis
22 was representative of national outpatient retail

1 pharmacy usage patterns only. Inpatient use was
2 not captured in the analysis, which represented
3 28 percent of combination hydrocodone-containing
4 analgesics use. No statistical tests were
5 performed to determine any statistically
6 significant changes over time.
7 In summary, in year 2011, approximately
8 131 million prescriptions and 47 million patients
9 received combination hydrocodone-containing
10 analgesics. The number of prescriptions and unique
11 patients receiving combination hydrocodone-
12 containing analgesics far exceeds any other
13 selected opioid analgesic in this analysis.
14 Primary care practitioners prescribed about
15 40 percent of total combination hydrocodone-
16 containing analgesic prescriptions. Combination
17 hydrocodone- and oxycodone-containing analgesics
18 appear to be used more often to treat acute pain
19 conditions. Single ingredient opioid analgesics
20 appear to be used more often for the treatment of
21 chronic pain conditions.
22 Thank you.

1 DR. J. WOODS: Thank you, Dr. Gill.
2 Dr. Dormitzer.
3 **FDA Presentation - Catherine Dormitzer**
4 DR. DORMITZER: Good morning. My name is
5 Cathy Dormitzer, and I'm an epidemiologist in the
6 Division of Epidemiology within OSE.
7 Today I will be reviewing the high level
8 points of DEA's most recent eight-factor analysis
9 that asks FDA to reschedule hydrocodone products
10 from Schedule III to Schedule II. We focused on
11 how they analyzed the data. Then we did our own
12 analysis, and I will walk you through what they
13 did, what we did, and why we think our analysis may
14 be more appropriate.
15 DEA based its recommendation to reschedule
16 hydrocodone products on their analysis that found
17 that these products have an abuse potential that's
18 similar to oxycodone products. OSE, however,
19 concluded that hydrocodone combination products do
20 have lower rates of abuse compared to oxycodone
21 products when appropriate denominators are used.
22 And I will be walking you through OSE's analysis.

1 Both DEA and OSE found hydrocodone
2 combination products are widely abused, but as
3 mentioned earlier by Dr. Calderon, the CSA does not
4 stipulate a numerical threshold for abuse levels
5 for determining scheduling.
6 The second main finding that DEA presented
7 was that the addition of acetaminophen or another
8 analgesic product does not reduce the abuse
9 potential of hydrocodone combination products.
10 DEA did not provide data to evaluate the
11 claim, likely because there are no
12 single-ingredient hydrocodone products on the
13 market with which to directly compare the
14 combination products. We conducted an indirect
15 analysis using other opioids that have both single
16 ingredient and are also combined with acetaminophen
17 and found lower abuse ratios for the combination
18 products.
19 So now I'm going to walk you through how we
20 conducted these types of analyses. So how do we
21 compare drug abuse potential between products?
22 There are no national abuse surveillance systems

1 for pharmaceutical products. Abuse ratios, also
2 called abuse rates, are computed to adjust for drug
3 utilization. So we can compare between products.
4 But numerators and denominators come from different
5 data sources with different sampling methodologies
6 and different sampling populations, so these
7 estimates are crude, but they're our best measures
8 currently available.
9 Measuring drug abuse-related health outcomes
10 includes misuse and abuse, overdose, and death for
11 specific prescription drug products, and that's
12 quite challenging. The numerators are usually
13 limited as far as giving us estimates by substance,
14 composition, and formulation. Sources of data used
15 by DEA that provide estimates of morbidity and
16 mortality related to abuse are the Drug Abuse
17 Warning Network, also called DAWN; the National
18 Poison Data System, also called NPDS; and the
19 Florida Department of Law Enforcement Medical
20 Examiners.
21 There are also reported behaviors of abuse
22 that do not necessarily result in an adverse

1 medical event. They're simply self-reports of drug
2 abuse, and these data sources include National
3 Survey on Drug Use and Health -- it's also called
4 NSDUH -- and Monitoring the Future. I will provide
5 more details about these data sources later in the
6 talk.
7 There is no ideal denominator. The default
8 denominator is the U.S. population, but it does not
9 adjust for drug utilization. DEA and OSE differ on
10 the most appropriate choice, and the choice of an
11 appropriate denominator is key. For this analysis,
12 oxycodone, which is a Schedule II drug, was used as
13 a comparator. It has different -- it's different
14 than hydrocodone because it has different
15 formulations and compositions.
16 So let's talk more about using oxycodone as
17 a comparator. All hydrocodone products are
18 combinations. All are immediate release, and most
19 are in combination with acetaminophen. And
20 oxycodone is marketed as combination products,
21 which are all immediate release, but also single
22 ingredients that are immediate release and extended

1 release.
2 The highest milligram strength for
3 hydrocodone products is 10 milligrams. And the
4 highest strength for oxycodone is 80 milligrams.
5 And this difference is important and will be
6 discussed later.
7 So let's look at the similarities. They are
8 both opioid pain relievers. Both single-ingredient
9 products are Schedule II substances. They are
10 fairly equipotent on a milligram basis as an oral
11 analgesic. Both products are in combination mostly
12 with acetaminophen, and they have both been on the
13 market a long time. And they both have a high
14 volume of use.
15 But this is how they're different. Only
16 oxycodone has single-ingredient and extended-
17 release products on the market. And as Dr. Gill
18 previously presented, these compositions and
19 formulations are used differently than hydrocodone
20 combination products. Also, the number of
21 milligrams per dosage unit is different for some
22 oxycodone products, and that is important as shown

1 in the next slide.
2 This is a table that shows the differences
3 between products and how that relates to the
4 different denominators that are used in this
5 analysis. The first column shows the percent of
6 the total number of prescriptions by formulation
7 and composition, and the next column shows the
8 percent of the total amount distributed in
9 kilograms. Again, by formulation and composition.
10 As you can see, 100 percent of hydrocodone
11 prescriptions are combination products. And they
12 are also 100 percent of the kilograms distributed
13 or sold. With oxycodone, it's a different picture.
14 Thirty-one percent of the prescriptions dispensed
15 are a single ingredient, but that represents
16 73 percent of kilograms distributed. With
17 combination products, it's the opposite. Sixty-
18 nine percent of the prescriptions are combinations,
19 but these products represent 27 percent of the
20 kilograms distributed. That's because it takes
21 more kilograms of oxycodone to produce
22 single-ingredient products than it does to produce

1 the combination products.
2 So now let's talk about the numerators. As
3 mentioned previously, the majority of the existing
4 drug abuse data sources do not provide information
5 on specific products or brands in composition or
6 formulation. And that's a problem when examining
7 oxycodone products, but not for hydrocodone
8 products because they're all immediate release
9 combination products. And later when we are
10 discussing abuse ratios, it will become clear why
11 this is a problem.
12 These are the sources of data that measure
13 morbidity. DAWN provides national estimates on all
14 drug-related emergency room visits. It can provide
15 estimates by substance, composition, and
16 formulation, and no other data set is this
17 granular. NPDS, which is the National Poison Data
18 System, provides data on calls to poison control
19 centers nationwide. So it's not an estimate. It
20 provides data on all toxic exposure calls, but by
21 substance only.
22 There are no national sources that measure

1 mortality by specific opioid drug substances as a
2 cause of death other than for methadone. However,
3 at the state level, the Florida Medical Examiners
4 collects data on drug-related deaths in the state
5 of Florida. Drugs are usually analyzed by
6 toxicology screens, so these data are provided by
7 substance only and not by composition and
8 formulation.
9 The data on reported behaviors of abuse are
10 the National Survey on Drug Use and Health, also
11 called NSDUH, and it provides national estimates on
12 the non-medical use of prescription drugs by drug
13 classes, such as pain relievers, tranquilizers,
14 stimulants and sedatives.
15 Monitoring the Future is a national survey
16 that questions high school students and college
17 students on their drug-taking behaviors. This
18 survey asks about narcotics other than heroin and
19 also specifically about Vicodin and OxyContin, but
20 no other specific opioids. So it is not specific
21 by formulation and composition, really.
22 Now, the various data sources that are used

1 for denominators, which can also be thought of as
2 exposure opportunity. DEA and OSE both used
3 unadjusted rates and total number of prescriptions
4 in previous analyses. DEA in its most recent
5 eight-factor analysis used patient days of therapy
6 and number of kilograms sold. OSE extended their
7 analyses and included numbers of patients and total
8 number of tablets dispensed.
9 Now, I'm going to walk you through the
10 denominators and discuss the strengths and
11 limitations of each choice. The total number of
12 prescriptions assumes an equal amount of drug abuse
13 exposure opportunities for each prescription. The
14 strength is it adjusts for drug utilization, but
15 the limitation is that the number of tablets vary
16 between prescriptions and formulations,
17 compositions. And milligram strength vary by
18 product.
19 The total number of patients has been used
20 historically, sometimes referred to URDDs, or
21 unique recipient of drug dispensed. And the
22 assumption is that each person with a prescription

1 is the one that is at risk and assumes equal risk
2 for the person receiving one prescription as the
3 one receiving 12. The strength is it approximates
4 how many people are initially exposed to the drug
5 product. The limitation is the number of
6 prescriptions per patient varies considerably by
7 product and that patients with more prescriptions
8 may be more at risk for abuse themselves and may
9 increase the risk for others.
10 DEA in its last analyses used total patient
11 days of therapy, which is the total days of supply
12 across prescriptions. The assumption is that it
13 accounts for the differences in duration of therapy
14 between prescriptions. Its strength is that it
15 accounts for the variability introduced by the
16 differences in the number of days of therapy per
17 prescription.
18 The limitation is that it does not account
19 for differences in the amount of tablets per
20 prescription. Hydrocodone can be prescribed one to
21 two tablets every six hours, so that means roughly
22 four to eight tablets per day. So a month's supply

1 is roughly 100 tablets. And oxycodone could be
2 prescribed one every 12 hours, which would be two
3 tablets per day, and that would be 60 tablets per
4 month.
5 DEA also used total kilograms of drugs sold
6 as a denominator. The assumption is that the sales
7 from manufacturers to distributors account for all
8 drug products sold in the marketplace and that
9 1 kilogram of hydrocodone exposure opportunity
10 equals 1 kilogram of oxycodone exposure
11 opportunity. The strengths are it includes drug
12 lost in supply chain prior to prescription, in
13 transit or at the wholesalers and includes drug
14 diverted from pharmacies, hospitals and doctors'
15 offices. But the limitation is that 1 kilogram of
16 hydrocodone produces many more tablets than
17 1 kilogram of oxycodone. And I'll show you how
18 that works next.
19 Let's look at this table. The last column,
20 which tells us the number of tablets each kilogram
21 yields for hydrocodone and oxycodone products, is
22 an important one. As you can see, 1 kilogram of

1 hydrocodone combination products produces on
2 average 141,000 tablets, and 1 kilogram of
3 oxycodone produces 77,000 tablets of oxycodone.
4 So if we are to assume that each tablet of
5 drug represents an exposure opportunity, then that
6 means that 1 kilogram of hydrocodone is not the
7 same as 1 kilogram of oxycodone. And this gets a
8 little tricky, but it's important to remember that
9 when you have a large denominator, the resulting
10 ratio is low. And when your denominator is
11 smaller, it increases your ratio.
12 So OSE's position is that 1 kilogram of
13 hydrocodone does not equal the same number of
14 exposure opportunities as 1 kilogram of oxycodone.
15 And using this tablet, that would mean that there
16 are 141,000 exposure opportunities for hydrocodone,
17 but only roughly 77,000 exposure opportunities for
18 oxycodone. A caveat, these estimates are of
19 tablets per kilogram are approximations; they're on
20 average. But they're still informed, educated
21 averages.
22 As a result, OSE used a new metric, and that

1 is total number of tablets dispensed. The
2 assumption is that each tablet represents drug
3 availability and is an exposure opportunity for
4 abuse. The total number of tablets is obtained
5 from drug utilization databases. The strength of
6 this metric is that it accounts for variability due
7 to differences in the number of tablets per
8 prescriptions and days of therapy. But the
9 limitation is that it does not account for drug
10 diverted in the supply chain.
11 So in summary, there is no perfect
12 denominator, but we need to select one. Sales of
13 drug product in kilogram is DEA's preferred
14 denominator. And it does account for drug lost in
15 the supply chain prior to prescription, but it does
16 not account for prescribing composition and
17 formulations between these two drug products.
18 Total tablets dispensed is OSE's
19 denominator. It accounts for some differences in
20 prescribing, for differences in composition and
21 formulation between products, and OSE thinks it is
22 the most granular measure of exposure opportunity

1 for abuse. It does not, however, account for drug
2 lost in the supply chain prior to dispensing
3 prescriptions.
4 So we finally get to the results, which will
5 be presented as drug abuse ratios. It's important
6 to keep the following limitations in mind when
7 you're examining drug abuse ratios. These data are
8 not linked. Each data set has different sampling
9 methodologies, different populations, different
10 methods for calculating point estimates and
11 respective confidence intervals. And we cannot
12 compute confidence intervals on these intervals to
13 date so far.
14 Now, let's look at the total number of toxic
15 exposure poison control calls using different
16 denominators. As I stated earlier, when presenting
17 numbers of events without adjusting for drug
18 utilization, the default denominator is the U.S.
19 population. I am presenting one year of data, and
20 I'm doing this because these data have been
21 consistent for all the years analyzed.
22 The solid yellow bar represents hydrocodone

1 products, and the solid blue bar is for oxycodone
2 products. And as you can see, the number of toxic
3 exposure poison control calls was higher for
4 hydrocodone than for oxycodone.
5 So when abuse ratios was computed using
6 100 kilograms of drugs sold as a denominator, it
7 was still higher for hydrocodone. But when million
8 tablets dispensed was used as a denominator, things
9 changed. The abuse ratios for oxycodone products
10 is higher than for hydrocodone products.
11 Now, let's look at DAWN data, which provides
12 national estimates of abuse-related emergency room
13 visits. The data have been consistent from 2004
14 through 2010, so again, only one year of data are
15 presented. The solid yellow bar represents
16 national estimates for hydrocodone, and solid blue
17 bar is for all oxycodone products. DAWN can also
18 provide estimates for oxycodone by combination and
19 single ingredient. So the blue striped bar are the
20 national estimates for oxycodone combination
21 products, and the blue checkered bar is for
22 oxycodone single-ingredient products, and includes

1 both IR and ER formulations.
2 As you can see in this first graph -- and I
3 guess I'm hoping everyone knows that IR means
4 immediate release and ER means extended release,
5 and usually extended release have higher milligram
6 strength.
7 So as you can see in the first graph, the
8 total number of abuse-related ED visits for all
9 oxycodone products is higher than for hydrocodone
10 products. But when we split out the estimates
11 between combination and single-ingredient products,
12 they are both lower than for hydrocodone.
13 This next graph are abuse ratios. It shows
14 these same estimates of abuse-related ED visits
15 over 100 kilograms distributed. Now you can see
16 the abuse ratios for total oxycodone products are
17 only marginally higher than -- well, the total for
18 oxycodone is only marginally higher than for the
19 total hydrocodone products. But when we compute
20 the ratios for the combinations and the
21 single-ingredient products, the ratio for
22 combination products appears to be markedly higher

1 than for hydrocodone. And the ratios for the
2 extended release products looks the same as
3 hydrocodone, and this illustrates the effect that
4 denominators can have on an abuse ratio.
5 But this last graph shows the abuse ratios
6 using million tablets dispensed as the denominator.
7 The ratio for total oxycodone products are higher
8 than for hydrocodone products, as are the ratios
9 for combination and single-ingredient products.
10 When split out the ratio for the oxycodone
11 combination products, it's higher, but the
12 single-ingredient products are remarkably higher.
13 Now for OSE, its current thinking, DAWN is
14 the data set that provides the most granular level
15 of detail. It allows us to differentiate between
16 substance, composition and formulation. And that
17 is why it is the data set that OSE prefers to use.
18 So now let's talk about mortality. The
19 graph came directly from DEA's last eight-factor
20 analysis that was submitted to the HHS. DEA used
21 the data from the Florida Department of Law
22 Enforcement Medical Examiners of drug-related death

1 and computed the number of deaths attributed to
2 hydrocodone and oxycodone and used kilograms sold
3 as a denominator. This graph shows the abuse
4 ratios for these two products, and they appear to
5 be similar.
6 OSE did not analyze these data using our
7 preferred denominator because these data do not
8 differentiate between oxycodone deaths that were
9 associated with single ingredient versus
10 combination ingredient oxycodone.
11 So now let's look at behavioral outcomes,
12 which would be NSDUH data. OSE computed abuse
13 ratios using million tablets dispensed and using
14 NSDUH. If a respondent responded non-medical use
15 for the first time in their lifetime, the national
16 estimates of these first-time users, otherwise
17 labeled initiates, can be obtained. So now the
18 denominator is the number of tablets dispensed in
19 that year, and OSE computed abuse ratios.
20 As you can see, the data are equivocal. The
21 abuse ratios appear slightly higher for hydrocodone
22 in years 2, 3, and 5 but appear to be slightly

1 higher for oxycodone in 2004. But again, these
2 numbers are similar.
3 Monitoring the Future is a survey of school
4 attending adolescents and young adults on their
5 drug-taking behaviors. These are questions
6 specifically asking about Vicodin, oxycodone, and
7 narcotics that are not heroin. And so the
8 questions are very targeted.
9 There is a higher prevalence of the non-
10 medical use of Vicodin compared to OxyContin, and
11 we hypothesize that this is the result of more
12 availability of Vicodin. And even though the
13 survey showed that there were more high school
14 students reported trying Vicodin, we cannot link
15 reported use with measures of morbidity and
16 mortality.
17 DEA asserted that the non-narcotic active
18 ingredient added to hydrocodone combination
19 products did not deter abuse. There is no data to
20 examine this conclusion, and all hydrocodone
21 products are combination products. So OSE could
22 not examine this issue directly.

1 So we examined abuse ratios for two opioid
2 products that contain both single-ingredient and
3 combination products. Those two opioids were
4 oxycodone IR single ingredient and tramadol single
5 ingredient, which is also an IR product, and the
6 combination products.
7 Tramadol is not scheduled, and the abuse
8 ratios per million tablets were low. But as you
9 can see by both these graphs, the addition of
10 acetaminophen is associated with lower levels of
11 abuse.
12 So in summary, OSE agrees with DEA that
13 abuse ratios can be used to characterize abuse risk
14 for hydrocodone to compare with other opioid
15 products. Oxycodone combination products are the
16 most appropriate comparator. Abuse ratios are
17 highly dependent on numerator and denominator, and
18 OSE feels that the best data source to provide the
19 most granular level of detail is DAWN, and that the
20 best denominator to provide the most accurate
21 measure of exposure opportunity is number of
22 tablets dispensed.

1 Most data indicate that hydrocodone
2 combination products have lower abuse ratios than
3 oxycodone combination products, and that's despite
4 much larger prescription volume and exposure
5 opportunity. Data do not support DEA's assertion
6 that the non-narcotic active ingredient in
7 hydrocodone products do not reduce abuse potential.
8 OSE's indirect analysis from other opioid products
9 suggest lowered abuse ratios for combinations when
10 compared to single-ingredient products of the same
11 substance. The data here, however, do suggest that
12 hydrocodone products are widely abused. Thank you.
13 **Committee Questions to Presenters**
14 DR. J. WOODS: Thank you, Dr. Dormitzer.
15 Since we have a lot of questions, I imagine,
16 you might as well stay there, I think. And we can
17 ask the other presenters to come back to the podium
18 or to a microphone where they can be heard.
19 Dr. Cooper.
20 DR. COOPER: Yes. My question is for
21 Ms. Finegan from the Office of the Chief Counsel.
22 In your slide 20 in your presentation, you show us

1 the differences between or the three factors that
2 HHS considers when making the determination for
3 Schedule II versus Schedule III. Can you provide
4 clarification for us?
5 For example, does HHS require that all three
6 of those standards be met to move a drug to a more
7 restrictive category, i.e., Category II, or for
8 example, if there is evidence of severe abuse
9 potential, would that be sufficient to -- for HHS
10 to make the finding that it would require more
11 restrictions?
12 MS. FINEGAN: I believe there's a federal
13 court case that has held that all three findings
14 need not be met. But when I received my training
15 to work on controlled substances for the Office of
16 the Chief Counsel, I was told that DEA does prefer
17 that we try to make sure that all three findings
18 are met. And we usually try to do that when we
19 write up our eight-factor analyses.
20 I've never worked on one where we've said,
21 well, we've got two but not the third, but we're
22 going to put it in this schedule anyway. But

1 theoretically, it could be possible.
2 DR. J. WOODS: Dr. Suarez.
3 DR. SUAREZ-ALMAZOR: Yes. Thank you. I
4 have three questions, but they are straightforward.
5 The first one relates to the difference that was
6 shown with respect to the increasing use of
7 hydrocodone when weight is used versus number of
8 prescriptions. So it would seem that over time if
9 we used weight, there's more of an increase in
10 hydrocodone than if we just use the number of
11 prescriptions.
12 So I was wondering if that was related to an
13 increase in the number of pills per prescription
14 over time. If you look at the slide that had the
15 weight, they increased from 2007 --
16 DR. GILL: I think she's referring to the
17 kilogram slide.
18 DR. SUAREZ-ALMAZOR: I just made a note. I
19 didn't mark the slide number. Let me go real
20 quickly. It was the graph that you had for -- let
21 me see where this is -- using trends.
22 DR. DORMITZER: No, I think it's my slides.

1 You mean slide 23?
2 DR. SUAREZ-ALMAZOR: Let me look real
3 quickly.
4 DR. DORMITZER: Is that the one you're
5 talking about?
6 DR. SUAREZ-ALMAZOR: It was the -- no, you
7 had some graphs -- when you -- let me go real
8 quickly. It's number --
9 DR. DORMITZER: Or was it Rajdeep's?
10 DR. SUAREZ-ALMAZOR: -- number 5, weight in
11 kilograms of selected opioid analgesics sold from
12 manufacturers to channels of distribution.
13 So when we look at this one, the increase in
14 use appears to be greater than we look at the next
15 graph, which is number 10, where you're doing
16 number of prescriptions. So I was just wondering
17 if this was due to the fact that prescriptions over
18 time may be including higher number of pills. So,
19 for instance, two pills every six hours as opposed
20 to one pill every six hours.
21 DR. GILL: Let me see if I understand your
22 question completely. So number 5, you were trying

1 to compare number 5 and 10 in terms of --
2 DR. SUAREZ-ALMAZOR: Yes, number 5,
3 apparently there was an increase of 20 percent if
4 we look at weight, but if we look at prescriptions,
5 the increase is -- I mean, I would have to
6 calculate, but it's like 5 percent only. So it
7 would seem to me that over time the prescriptions
8 are including higher dosages.
9 DR. GILL: Well, number 5 shows the weight
10 in kilograms that's going towards retail,
11 nonretail, all types of settings. But when we go
12 to slide number 10, it only shows prescriptions
13 that are being dispensed to U.S. outpatient retail
14 pharmacies only. So that could be one possible
15 reason for a difference in amount of change that
16 you are referring to.
17 DR. SUAREZ-ALMAZOR: Yes, but the proportion
18 in weight is larger than the proportion in
19 prescriptions, so that's -- I mean, unless there's
20 more that's going out of retail but that --
21 DR. GILL: I don't think we can directly
22 compare that. This is -- let's say we are saying

1 this increased 20 percent and the prescriptions
2 increased 10 percent, we can't directly compare
3 these two slides just by the nature. This is
4 kilograms being dispensed. This is actually the
5 total sales that's going to all the channels of
6 distribution, whether it's retail, nonretail, the
7 whole --
8 DR. SUAREZ-ALMAZOR: We don't know then if
9 the prescriptions have changed over time and the
10 number of pills per prescription is larger than now
11 than what it was before. We don't have that data.
12 DR. GILL: The number of prescriptions have
13 increased from --
14 DR. SUAREZ-ALMAZOR: The number of pills per
15 prescription?
16 DR. GILL: Pills per prescription, we did
17 not analyze that.
18 DR. SUAREZ-ALMAZOR: Because that's what, to
19 me, the data would suggest indirectly.
20 DR. GILL: No, we have not looked at that.
21 DR. SUAREZ-ALMAZOR: And my other question
22 that's related to this, also, one of the

1 differences between Schedule II and Schedule III is
2 the refills that are allowed. So I was wondering
3 if we had data on refills and whether we know if
4 the majority of prescriptions for hydrocodone are
5 actually with six months' refills or just single
6 time prescriptions. Is there any data at all on
7 that?
8 DR. GILL: No, the prescription data that we
9 showed in slide 10 does include total number of
10 prescriptions, which is new and refills, but of
11 course, the other ones are just by the nature that
12 they are controlled, too, so most of the times,
13 they are just new prescriptions.
14 DR. SUAREZ-ALMAZOR: And then my last
15 comment very quickly, it would seem to me from the
16 data you've presented that using just the number of
17 tablets as the nominator, it inherently creates a
18 bias towards oxycodone because the dosage of
19 oxycodone is per tablet. I mean, they are tablets
20 that have a higher dosage than hydrocodone. So to
21 me, that would create a bias because the
22 denominator, it's always going to be smaller for

1 oxycodone because of the dosage.
2 So I mean, if you are prescribing 10
3 milligrams of hydrocodone, you may prescribe eight
4 pills per day. If you are prescribing 20
5 milligrams of oxycodone, you may prescribe one pill
6 a day or two pills a day.
7 DR. DORMITZER: That's right, and
8 that's -- in other words, you were -- there's no
9 way -- I guess there's no real way to have data on
10 abuse ratios by number of milligrams available to
11 the patient. I guess but the number of milligrams
12 per pill does provide insight into abuse potential.
13 I mean, because what we are seeing is that the
14 single-ingredient products, which even the
15 single-ingredient immediate release -- and,
16 Rajdeep, you're going to have to back me up
17 here -- do have higher milligram strength than the
18 combination products. The single-ingredient, they
19 do have higher milligram strength.
20 DR. SUAREZ-ALMAZOR: So you have less pills.
21 So that's why I think there's an inherent bias
22 that's created by using that as a denominator, as

1 opposed to weight where you are using the actual
2 number of milligrams that have been dispensed.
3 DR. STAFFA: If I could help clarify here, I
4 think that's why we think the comparing to the
5 oxycodone combination products specifically is a
6 more appropriate comparator because the dosing and
7 the usage is much more similar as is the
8 prescription size. That's why we're uncomfortable
9 with comparisons that would include the
10 single-ingredient oxycodone in there because you're
11 right, they are very different in their composition
12 and in their nature.
13 DR. SUAREZ-ALMAZOR: But if I understand the
14 data, you only have that for the numerator, not for
15 the denominator.
16 DR. STAFFA: Actually, we're able to
17 differentiate the denominator for tablets dispensed
18 only for those products, yes. We're able to do
19 that with the DAWN analysis.
20 DR. J. WOODS: I want to remind the FDA
21 staff especially to identify themselves for the
22 scribe. It's very important for all of us.

1 DR. STAFFA: Sorry. My name is Judy Staffa
2 from Division of Epidemiology.
3 DR. J. WOODS: Dr. Hernandez-Diaz.
4 DR. HERNANDEZ-DIAZ: A question also for
5 Dr. Gill regarding the trends. Even this trend is
6 pretty flat, and I have some publications that show
7 trends for specific populations in the U.S. from
8 2000 to 2007, 2008 that suggest an exponential
9 increase in hydrocodone or opioids use of like
10 300 percent, so three or fourfold in the years
11 around 2000 to around 2007.
12 Can you comment on the potential trends? Do
13 you have data before 2007?
14 DR. GILL: Not with me right now. Are you
15 interested in looking at -- going back a few years
16 or --
17 DR. HERNANDEZ-DIAZ: Well, I think it might
18 be interesting for the discussion later today or
19 tomorrow that if there has been a trend in the use
20 of opioids that has not been -- at the same time as
21 a reduction in the use of other analgesics, then it
22 would suggest that either pain is increasing in the

1 U.S. or there is an increase in use of painkillers
2 for good medical reasons or medical abuse or non-
3 medical uses. So I think the trends might be
4 important for the discussion, and that's why I was
5 wondering about potential trends before 2007.
6 DR. GILL: No, in this analysis, and also,
7 there's a background document. We only have gone
8 back pretty much five years for all the opioids
9 that we selected. I'm not sure if we have other
10 publicly available data that we are able to share
11 at this meeting today or tomorrow going back
12 another five years.
13 DR. J. WOODS: Dr. Morrato.
14 DR. MORRATO: Thank you.
15 I had one clarifying question for Dr. Gill
16 and one for Dr. Dormitzer. I'm wondering if
17 you -- we were talking a little bit about refills
18 and the difference between the Class II and the III
19 or different requirements there. Do we have any
20 data on the proportion of prescriptions that are
21 refilled between the drugs? I know that you have
22 cumulative data incorporated in both the primary

1 and secondary, but what proportion of the index, if
2 you will, prescriptions are refilled for the --
3 DR. GILL: No, we did not look at that, but
4 hydrocodone does -- hydrocodone combination
5 analgesics does show a total, which is of course
6 new and refills. But, no, we do not have the
7 proportion.
8 DR. MORRATO: Can you calculate it? You
9 just -- with the data that you have? It might help
10 us understand the impact on burden by switching to
11 differences in the requirement.
12 DR. GILL: I'm sure we can do it in the
13 future, but I don't know if we can do it real quick
14 and share publicly. I'm not sure.
15 DR. STAFFA: Yes, this is Judy Staffa again.
16 I think that, right. We did not look at new and
17 refill for hydrocodone. But if you look at the
18 distribution of days of therapy when you add it
19 across patients, the fact that the median is only
20 eight days kind of gives you a suggestion that many
21 of these are new prescriptions. But it's not
22 something we looked at.

1 DR. MORRATO: Did you look at the histogram
2 as well? I mean, I know we got -- are you seeing
3 pretty tight, or are you seeing sort of a bimodal?
4 DR. STAFFA: Well, there's a pretty -- it's
5 actually -- it's not tight, and there's a lot of
6 outliers. So that's why I can't really say exactly
7 the percentage that are refills.
8 DR. MORRATO: Do you know what -- well, we
9 don't have the data here. It would be useful to
10 know what proportion are these outliers that are
11 representing probably the multiple refills, which
12 is I think what you're getting at, because that
13 gives us maybe an indirect estimate on the number
14 of patients that might be impacted by the schedule
15 differences.
16 The other question I had for Dr. Dormitzer,
17 which I really appreciated your presentation around
18 data source and denominator and numerator. And I'm
19 wondering if there's any information that would
20 inform us on what proportion might be lost in the
21 distribution chain. You were saying that that was
22 a strength of using the kilogram because it

1 incorporates all of the drug as opposed to just
2 what's dispensed. So is that a concern for us,
3 that there is a significant amount lost in the
4 distribution chain?
5 DR. DORMITZER: I really have no data or I
6 really don't know how much is lost in the supply
7 chain. But the one thing that I would say is that
8 when the National Survey on Drug Use and Health
9 asked about the non-medical use of the opioids,
10 they also had questions on the source, how did you
11 get these data. And I think it was like 80 percent
12 got the data -- and I don't want to actually -- I
13 don't want to quote percentages, exact percentages,
14 but a large proportion of non-medical users either
15 got their drug from their own doctor or from a
16 family or friend who also got their prescription
17 from a doctor, so in other words, from
18 prescriptions.
19 So we do know that prescriptions is a source
20 of drug that's resulting in drug abuse. But I
21 don't have percentages -- but I know it's a large
22 proportion. A large proportion was from either

1 their own doctor or from a friend or family's
2 doctor.
3 DR. MORRATO: Maybe this is something that
4 the DEA speaker could address. I'm wondering if --
5 DR. DORMITZER: I can get one slide
6 on -- but go ahead. Sorry.
7 DR. MORRATO: I'm wondering if the kilogram
8 is the norm that we use for many other illegal
9 drugs, such as cocaine, et cetera, so it's a
10 denominator of convenience in which maybe there is
11 a lot more lost in the distribution channels, if
12 you will, for those drugs. So if the DEA person
13 could comment on it, that would be helpful.
14 DR. J. WOODS: Thank you.
15 For a West Coast perspective, Dr. Mendelson.
16 DR. MENDELSON: Yes. Hi, Jim, how you
17 doing?
18 John Mendelson here. So one factor that may
19 explain the discrepancy between the kilograms
20 dispensed and the number of prescriptions is that
21 HMOs require patients often to get a three-month
22 supply of medication. And I have no idea whether

1 you can capture that in your epidemiologic data,
2 but a lot of us have felt over time that the reason
3 that there are more hydrocodone tablets sitting
4 available for people to divert or to be abused is
5 because patients have a substantial cost saving if
6 their prescription is filled through Merck Medco or
7 Caremark, or one of the large prescription -- the
8 mail-in pharmacies for the HMO.
9 I don't know if you have any data on that,
10 but it'd be very interesting to split that out.
11 Recently, they've eased up on that requirement for
12 opiates, at least in our area so that we don't have
13 to -- the patients -- the cost difference can be
14 substantial for a patient if they go to a local
15 pharmacy and fill their prescription in a one-month
16 interval versus go to Merck Medco and fill it at a
17 three-month interval. And so there's a lot of
18 pressure on the docs from everybody, except the
19 physician, to go for the three-month prescription.
20 If you have any way to split that out, that
21 would be absolutely fascinating, and that could
22 really terminate quite a bit of diversion and abuse

1 by not requiring such massive prescriptions to be
2 filled in order to save a little money.
3 DR. J. WOODS: Dr. Kaboli.
4 DR. KABOLI: Yes. I have a question for
5 Dr. Dormitzer on slide 28, if you can pull that one
6 up. So I think you did a very nice job both
7 presenting and then in the materials that I read
8 ahead of time about trying to differentiate what is
9 the numerator, what is the denominator. And it
10 makes a big difference depending on how we're doing
11 this.
12 So the abuse ratio is not something I'm
13 familiar with as a measure. So with these slides
14 that I'm looking at saying, well, I can see,
15 depending on how you do it, the abuse ratio could
16 go towards one or the other product. Is there an
17 acceptable abuse ratio that we could draw a line
18 here and say that this difference is somehow
19 meaningful?
20 DR. DORMITZER: No, and I guess that's one
21 of the reasons why we have -- I'm not trying to be
22 flippant, but this is one of the reasons for this

1 advisory committee because there is no standard
2 that I'm aware of in the CSA or --
3 DR. KABOLI: I didn't know if there were
4 other drugs that would have -- you could compare to
5 that would have an abuse ratio that we think is
6 acceptable.
7 DR. DORMITZER: Well, an acceptable ratio is
8 zero. But, I mean, no, it is higher for other
9 opiates, especially the single ingredients, but no.
10 DR. KABOLI: And the reason I ask is because
11 it seems like you could support just -- depending
12 on how you use the numerator and denominator, you
13 could support either argument as to whether there's
14 a difference. But, ultimately, is it for support
15 or illumination?
16 DR. DORMITZER: I actually think the only
17 thing -- and this is just my personal opinion, not
18 the opinion of FDA's. But the purpose of using an
19 abuse ratio is to compare between products because
20 now we are adjusting for drug utilization. That's
21 what the abuse ratio is for. It's to compare
22 between products. It's not necessarily the

1 one -- an excellent measure of abuse liability by
2 itself. So this is to compare between products.
3 That's why we calculated it. It's the between
4 products part.
5 DR. KABOLI: Thank you.
6 DR. J. WOODS: Thank you. Dr. Maxwell.
7 DR. MAXWELL: Thank you. I had two
8 questions, and Dr. Mendelson took care of one of
9 them. One of the other I have -- and whether
10 Dr. Calderon answers it or whomever. One of the
11 data sets that was not mentioned that concerns me
12 is the National Forensic Laboratory Information
13 system of DEA tells us how much of these various
14 controlled substances are being seen in the tox
15 labs. And maybe DEA can present it, but that is a
16 major picture of what's on the street, what's being
17 seen in medical examiner cases and what's being
18 identified in the labs. And I think that's a
19 picture that we need to consider, also.
20 DR. DORMITZER: I don't want to speak for
21 the DEA because this is really DEA's data set. I
22 can speak to -- when we were looking at the

1 eight-factor analysis, we did not do too much
2 analysis of the NFLIS, National Forensic
3 Investigative Survey --
4 DR. MAXWELL: Laboratory Information.
5 DR. DORMITZER: Laboratory Information
6 System. But can we get the backup slides, on my
7 backup slide, slide 21? And actually,
8 slide -- well, 21, 22 and 23. Because we realize
9 there might be questions about things that we
10 didn't do. And basically, the reason why we did
11 not examine NFLIS was, first of all, it's a law
12 enforcement survey, not public health.
13 DR. MAXWELL: -- medical examiners -- it
14 does include medical examiners --
15 DR. DORMITZER: And we also examined DAWN
16 medical examiner data. But the problem with the
17 medical examiner data is that it's by substance
18 only. So it's either hydrocodone or oxycodone.
19 And with the oxycodone, you have the
20 single-ingredient products as well as the
21 combination products. And there's absolutely no
22 differentiation between the two.

1 Slide 23? Okay. Still not up. But then
2 when we looked at the number of drug
3 reports -- that would be slide twenty -- it should
4 be slide 23. So now we're getting to --
5 (Pause.)
6 DR. MAXWELL: Well, you've got Stride up
7 there.
8 DR. STAFFA: It's before the Stride, Cathy.
9 It's prior to the Stride.
10 DR. DORMITZER: It should be slide 23 on my
11 backups because that's what I've written down.
12 DR. MAXWELL: Say it out loud.
13 DR. DORMITZER: These are my backup slides?
14 Slide 4. But then I should have also had reports.
15 The next one. There.
16 Now, what we're seeing here is
17 that -- again, but this is very equivocal because
18 now when we're talking about are the drug reports.
19 Is someone from DEA here? Okay. And what we see
20 is that it's actually higher -- I mean, they're
21 very similar, and they're sometimes higher for
22 oxycodone and sometimes higher for hydrocodone.

1 And this is a nationwide number of reports.
2 So again, the difference between these two
3 products was not remarkably high.
4 DR. MAXWELL: Thank you.
5 DR. DORMITZER: But these are the seizures.
6 These are the people who got caught, not the people
7 who distributed and didn't get caught.
8 DR. MAXWELL: Let me clarify because I spent
9 a lot of time with this. These are the
10 items -- these are the cases that have been turned
11 in to forensics -- whether it's a DEA lab or a
12 medical examiner or a local law department lab,
13 these are the items that have been identified.
14 DR. DORMITZER: Yes.
15 DR. J. WOODS: I'm going to caution
16 everybody to sort of shorten it up. I love those
17 yes/nos.
18 Dr. Crawford.
19 DR. CRAWFORD: Thank you, Mr. Chairman.
20 I think that the little series that I'm about to
21 ask is mostly yes/nos, mostly.
22 This is for Dr. Dormitzer first, but you may

1 be able to answer each of them. As I'm looking at
2 your slides, they don't need to be brought up, but
3 slide 20 on the unique recipients for drugs
4 dispensed, URDDs, that is the assumption that
5 there's one prescription set per patient, if I
6 understood correctly, when we use that data source.
7 And I appreciate each of the FDA speakers told us
8 it's separate data sources we're looking at.
9 Yet when I look at slide 32, on the
10 Monitoring the Future, I guess I'll ask you this,
11 is that behavioral data source, more prescriptions
12 more availability in the homes, for that data
13 source, is there the presumption that it's not a
14 unique recipient for the drugs dispensed?
15 DR. DORMITZER: Well, the unique recipient
16 is basically if someone has one prescription or 12
17 prescriptions, they count once. With Monitoring
18 the Future, the question -- these are survey
19 questions on their non-medical use of these
20 products. So they may or may not have had a
21 prescription at some point, or their friend may or
22 may not have had a prescription.

1 But the thing with Monitoring the Future,
2 they ask about Vicodin, OxyContin, and narcotics
3 other than heroin. Those are the three categories,
4 and that's it.
5 DR. CRAWFORD: I understand. Thank you.
6 DR. DORMITZER: And which makes sense
7 because with high school students, if you ask them
8 about hydrocodone combination products, they may
9 not know what you're talking about. So yes, the
10 number of students that reported non-medical use of
11 Vicodin was higher than for OxyContin, but those
12 were the only two drugs that were specifically
13 asked about.
14 DR. CRAWFORD: Thank you. And as we were
15 looking at the abuse ratios -- I believe your slide
16 is 28 and 29. But it's a more general question
17 that's based on the sale, the kilogram total sales,
18 or the tablets dispensed within the legitimate U.S.
19 supply chain. And this is a little take off of
20 questions asked by Dr. Morrato and Dr. Maxwell.
21 Are there any data sources available that
22 would also capture abuse from Internet and other

1 non-legitimate sources of procurement? And whether
2 those would differ between oxycodone products and
3 hydrocodone products.
4 DR. DORMITZER: There's one slide that I'll
5 be able -- because it already has been cleared and
6 has been presented at other advisory committees.
7 When the National Survey on Drug Use and Health
8 asked about how did you obtain the drug that you're
9 misusing, the overwhelming majority either reported
10 their source as a prescription themselves or they
11 got it from a friend or family member.
12 So then after saying that they got it from a
13 friend or a family member, which means they did not
14 have that prescription, someone else did, the
15 friend or family member had obtained the drug from
16 a doctor.
17 So I'll be able to get that slide and bring
18 it over here, but, basically, it was a large -- I
19 don't want to quote percentages, but it a large
20 proportion was coming from prescriptions rather
21 than from -- even if they -- well, I'm going to not
22 speculate whether they got it from the Internet.

1 But the Internet actually was remarkably low. But
2 I can definitely get that slide to you and just do
3 a real fast pop-up.
4 DR. CRAWFORD: Thank you.
5 DR. J. WOODS: I'm going to take the chair's
6 prerogative. We've got five more questions to
7 answer, and we're 15 minutes behind. So I'm going
8 to go ahead with Dr. Walsh. We're going to try to
9 pick up those questions and get a cup of coffee,
10 but while Dr. Walsh is coming up, maybe we could
11 have one more question real quick like.
12 Dr. Jones.
13 DR. JONES: So a combination of questions
14 and comments around the prescription refills for
15 hydrocodone. I ran a quick analysis before coming
16 up. It was about 20 percent from IMS MPA data, but
17 I wasn't able -- just didn't have time to look at
18 was it one refill, two refills, three refills. But
19 I think it's a really important issue as far as
20 access because if, say, it's 99 percent that had
21 three refills or less, you're potentially
22 mitigating that even if you move it to Schedule II

1 because they're able to do prescriptions over a
2 90-day period. So I think understanding what that
3 could do for access is really important.
4 A couple of other questions, DAWN ME, you
5 actually can get drug product specific information
6 in the DAWN medical examiner data set. So I would
7 maybe talk to SAMHSA about the file.
8 I know the numbers are relatively low, but I
9 still think it does provide 13 states, at least for
10 2010, where you could get information,
11 product-specific information.
12 DR. DORMITZER: We actually did look at DAWN
13 data. It's also in my backup slides, but it's the
14 first of my backup slides. And basically, when we
15 did look at DAWN medical examiner data, we looked
16 at the states where they had -- it's a consistent
17 panel. In other words, they work -- they had the
18 entire -- all the medical examiners in each
19 state -- and there were six states. And I forgot
20 which ones they were. They were, I don't know,
21 Maryland, Vermont, New Hampshire, New Mexico and
22 Massachusetts.

1 Anyway, so this is compiling all six states,
2 the number of deaths, so they're just numbers.
3 They're not estimates. And then as you can see,
4 the yellow bars are hydrocodone, the blue,
5 oxycodone. As you can see, they're much higher for
6 oxycodone than they are for hydrocodone.
7 The thing is that the oxycodone, we don't
8 know how many were the result of single-ingredient
9 products or combination products. And then with
10 both hydrocodone and oxycodone, most of them were
11 the result of multiple deaths.
12 So like one drug only, it was only 4 percent
13 of the deaths, one drug only for hydrocodone were a
14 single ingredient or not single ingredient, one
15 drug. In other words, just hydrocodone. And then
16 for oxycodone, it was 12 percent.
17 So it's higher, but most of -- like I said,
18 for both hydrocodone and oxycodone, most were the
19 result of multiple drugs. But for single drug
20 death -- and single drug, I just mean hydrocodone
21 combination or oxycodone single or combination, it
22 is higher, single drug for oxycodone than

1 hydrocodone. But these data do not differentiate.
2 These are the result of tox screens, so this is
3 where we're not getting that information from the
4 data.
5 DR. JONES: There is a variable, though, for
6 brand name in the DAWN medical examiner data set.
7 DR. DORMITZER: It's a single versus
8 multiple drug.
9 DR. JONES: Because you can look up like
10 Opana or OxyContin. You can look up those types of
11 things.
12 DR. DORMITZER: In the medical examiner
13 data?
14 DR. JONES: Yes. In the file that we have
15 at CDC, you can do it. I just -- I'm not -- I
16 don't know how many are missing where maybe it just
17 listed as an oxycodone combination, but there is in
18 the dictionary a brand name file.
19 DR. DORMITZER: Well, yes, but that's for
20 the medical -- that's for the -- that's the drug
21 reference vocabulary. That's for the emergency
22 room visits. And with the emergency room visits,

1 sometimes we do have very specific data. But other
2 times, it depends on what the physician writes
3 down. Are they writing down Opana or oxymorphone?
4 DR. JONES: Right.
5 DR. DORMITZER: So that depends. But this
6 is medical examiner data. So now this is
7 not -- unless the pill bottle is right next to the
8 patient or deceased, they don't have that level of
9 information. So this is for what were the drugs
10 present in the decedent.
11 DR. JONES: Right. I'll have to go back and
12 look. I thought that our data set had three
13 different categories of ways that the drugs are
14 defined, so I just have to go back. But I agree on
15 the single-ingredient deaths, oxycodone certainly
16 is higher than hydrocodone.
17 DR. DORMITZER: Yes. This is a consistent
18 panel. These are six states. And as you can see,
19 the numbers are fairly low. These are counts.
20 There are not even estimates. But it's a complete
21 count, so they're fairly low. So it would be
22 difficult to get an epidemiological assessment

1 because sometimes they would have that information,
2 sometimes they wouldn't. But this is what's
3 reported on from -- it is reported by substance.
4 DR. JONES: Yes, I think the same
5 limitations would exist for DAWN ED as far as did
6 they list it as a brand name or is it oxycodone or
7 oxycodone combination.
8 DR. DORMITZER: Well, yes, but at least with
9 the emergency room visits, we can combine. If they
10 wrote down Percocet or if they wrote down oxycodone
11 combination, we can combine that to get one
12 estimate.
13 DR. J. WOODS: The chair's prerogative,
14 let's settle it on break.
15 Dr. Walsh, entertain us.
16 **Presentation - Sharon Walsh**
17 DR. WALSH: Thank you, Dr. Woods, and thank
18 you, committee members. It's a pleasure for me to
19 have the opportunity this morning to speak with
20 you. I'll try to make it brief since we are
21 running behind schedule. The title of my talk is
22 Abuse Potential of Hydrocodone in Human Studies,

1 and my name is Sharon Walsh from the University of
2 Kentucky.
3 This shows the outline for my presentation.
4 I'm going to start by simply providing definitions
5 for abuse potential versus abuse liability. I'm
6 then going to describe the methodological approach
7 that is used in the human laboratory to study abuse
8 potential with respect to populations and methods.
9 I'm then going to share the results of some
10 recently published studies that have examined
11 hydrocodone in the laboratory in normal volunteers
12 and in opioid-abusing individuals. And finally,
13 I'll summarize the results of these studies and
14 hopefully leave you with a few succinct take home
15 messages.
16 I know that for many of you, you're already
17 familiar with some of these concepts, but I want to
18 provide a brief background for those in the
19 audience that may not be. With respect to the
20 definition of abuse potential, abuse potential
21 characterizes the ability of a central nervous
22 system active drug to produce positive psychoactive

1 effects. These can include sedation, euphoria,
2 perceptual and other cognitive distortions,
3 hallucinations and mood changes. These effects are
4 viewed as correlated with or predictive of the risk
5 of abuse and/or addiction.
6 With regard to abuse liability, this term is
7 similar to abuse potential and sometimes they are
8 used interchangeably, but in fact, abuse potential
9 is just one part of abuse liability. Abuse
10 liability captures other factors, including, for
11 example, the ease of synthesis and drug abuse or
12 diversion history of that drug or similar related
13 drugs. So abuse liability actually describes abuse
14 potential in a social and public health context.
15 So how are these constructs measured? Abuse
16 potential is measured in the laboratory. In
17 animals, these studies usually involve self-
18 administration studies of the drug that is being
19 tested and also physical dependence testing. These
20 studies are also done in human volunteers, and
21 those typically involve direct drug administration
22 of the drug in question.

1 Abuse liability is also measured in the
2 community, and those data can include surveillance
3 data from various reporting sources such as
4 hospitals, treatment centers, national surveys and
5 medical examiner deaths, as you've already heard
6 about this morning.
7 So the next two slides will just provide
8 some brief background on the general methods that
9 are used in these studies. Typically, abuse
10 potential studies enroll adult healthy volunteers
11 with appropriate drug use histories, and
12 preferably, they're enrolled as inpatients so that
13 they can be confined for the duration of the study
14 in order to prevent any illicit or intervening
15 other drug use.
16 For studies of hydrocodone, the appropriate
17 population would be those with opioid abuse
18 histories but who are currently without physical
19 dependence on opioids. The studies include tests
20 of appropriate control conditions for comparison
21 with the test drug of interest, and it's ideal if
22 available to include both positive and negative

1 controls.
2 In the case of hydrocodone, the positive
3 control condition would obviously be another full
4 mu opioid agonist. And in all these studies,
5 double-blind testing is employed so that neither
6 the participant nor the observer knows what is
7 being administered on a given day.
8 In these studies, a comprehensive array of
9 outcomes is collected, and these can include
10 physiological measures such as effects on
11 respiration, cardiovascular systems, and pupil
12 diameter, which we use for most opioid studies
13 because it's exquisitely sensitive to mu opioid
14 agonist effects.
15 A battery of subjective measures are
16 incorporated that are presented to the subjects in
17 order to get an assessment of what their internal
18 state is, the experience that they're having with
19 the drug that cannot be observed. And these can
20 include visual analog questionnaires, adjective
21 scales, and street value estimates. We also can
22 collect observer-rated effects from the observers

1 who are blind to condition. And finally, cognitive
2 and psychomotor tasks can be included in order to
3 assess impairment.
4 I will tell you that all the studies I'm
5 going to present included a very comprehensive
6 array of outcomes. However, I'm going to limit the
7 presentation to just a couple of key outcomes for
8 the sake of time.
9 So there have been six human abuse potential
10 studies of hydrocodone that are contemporary that
11 were published between 2003 and 2010. Five of
12 these studies examined the effects of hydrocodone
13 when given orally. One examined hydrocodone and
14 homatropine in the Hycodan formulation. Three
15 examined hydrocodone in combination with
16 acetaminophen. One examined hydrocodone alone.
17 And then the last study examined the effects of
18 hydrocodone when given intravenously as a single
19 product.
20 All these studies employed within subject
21 and crossover designs. And those that have an
22 asterisk next to them were conducted in healthy,

1 non-drug using volunteers rather than opioid
2 abusers.
3 So this slide is the first of the studies,
4 and this is a study that was done by Jim Zacny at
5 the University of Chicago. And I'm going to take
6 one moment and walk you through the layout of the
7 slide because the following slides will be
8 similarly formatted. So the outcome is shown in
9 the title of the figure, so pupil diameter, and
10 then how much do you like the drug, which is a
11 visual analog questionnaire. The score is shown
12 along the Y axis, and the dose is shown along the
13 X axis.
14 In this study, Dr. Zacny examined a range of
15 doses of Hycodan and compared those to a single
16 dose of morphine at 40 milligrams and also included
17 a single dose of lorazepam, the benzodiazepine, as
18 a control condition for the potential sedative
19 effects of homatropine.
20 What you can see is that hydrocodone at 5,
21 10 and 20 milligrams in combination with
22 homatropine produced dose-dependent and significant

1 decreases in pupil diameters, as would be expected
2 for a full mu opioid agonist. The highest dose,
3 20 milligrams, produced effects that were
4 comparable to 40 milligrams of morphine, and
5 lorazepam had no effect on this outcome.
6 In the slide on the right side, you're
7 looking at scores for visual analog questionnaire
8 that poses the question to the subject, how much do
9 you like the drug. And this is a standard abuse
10 liability measure used in these studies. In this
11 case, Dr. Zacny is using a bipolar scale where 50,
12 a score of 50, is considered neutral, and anything
13 above 50 is an endorsement by the subject that they
14 do like the drug; and anything that would fall
15 below 50 would be an endorsement that they dislike
16 the drug.
17 You can see that placebo is hovering near
18 the neutral line and that hydrocodone produced
19 dose-related increases again with 20 milligrams,
20 the highest dose, being equivalent to 40 milligrams
21 of oral morphine. Lorazepam produced some
22 increases compared to placebo, but these failed to

1 reach significance.
2 This is another study by Dr. Zacny and his
3 colleagues, and in this study, they examined the
4 hydrocodone acetaminophen product, again, in
5 healthy volunteers. You can see that they examine
6 a range of doses for hydrocodone at 5, 10 and
7 20 milligrams, again including the 40-milligram
8 morphine dose as a comparison.
9 In this study, they also included a thousand
10 milligram dose of acetaminophen as a control. The
11 doses of hydrocodone are in white, and the doses of
12 acetaminophen are in yellow. And again, as in the
13 last study, you can see that hydrocodone produced
14 dose-dependent and significant decreases in pupil
15 diameter similar to morphine and dose-dependent
16 increases in ratings of liking that were highest
17 for the highest dose and equivalent to morphine at
18 40.
19 This is a study, the final study by Jim
20 Zacny in which they compared doses of hydrocodone
21 to doses of oxycodone, both of which were given as
22 combination products in combination with

1 acetaminophen. The doses that they selected were
2 oxycodone at 10 and 20 milligrams and hydrocodone
3 at 15 and 30 milligrams. You can see that, again,
4 hydrocodone produced dose-related decreases in
5 pupil diameter and that these were comparable to
6 those produced by oxycodone over this dose range.
7 In this slide, you're looking at ratings of
8 liking. And you can see that oxycodone effects
9 were significantly elevated above placebo, but they
10 were not dose dependent. And although there's some
11 elevation of scores with hydrocodone, these failed
12 to reach statistical significance.
13 These are other outcomes from that same
14 slide looking at oxycodone and hydrocodone in
15 combination with acetaminophen. The first are peak
16 scores on ratings of coasting, and coasting is a
17 pleasant feeling of relaxation that is endorsed by
18 opiate abusers when they have a good high. And on
19 the right-hand side are ratings of nausea. And you
20 can see that, essentially, oxycodone and
21 hydrocodone look identical on these two measures in
22 that they both produce increases in ratings of

1 coasting and also increase nausea in this non-drug
2 abusing cohort of volunteers.
3 This next study is one that we conducted in
4 our laboratory, and in this study, we examined
5 oxycodone, hydrocodone and hydromorphone. In all
6 cases, the drug was given orally, and this
7 was -- they were administered to a cohort of
8 prescription opioid abusers who again were not
9 physically dependent during the time of their
10 participation.
11 This slide is formatted a little differently
12 here because you're looking at time course, and
13 this allows you to see the relative onset of the
14 drug effects, the time to peak and the decline in
15 drug effects along with the dose responsive nature.
16 And this is data for the visual analog scale, how
17 much do you like the drug, and in this case, it's
18 actually a unipolar scale that ranges from zero to
19 100 with zero being no liking and 100 being the
20 highest score.
21 You can see that in all three cases, the
22 onset of drug effect is apparent within about the

1 first half hour to hour after oral administration.
2 The peak effects are occurring around one and a
3 half hours, and we can see a decline thereafter.
4 The highest dose of each of the drugs produces a
5 more sustained response. And in each case, the
6 effects were generally dose related for oxycodone,
7 hydrocodone and hydromorphone.
8 These are data from the same study, but
9 they're plotted a little bit differently. Here
10 you're looking at peak reduction scores for pupil
11 diameter and respiratory rate. But in this case,
12 the X axis is logarithmic, and that's because we
13 did not test the same identical doses or range of
14 doses.
15 At the start of this study, we actually were
16 very interested in trying to provide relative
17 potency estimates among the three drugs, and in
18 order to do that, we needed to confirm that we were
19 producing effects that were of generally equivalent
20 magnitude. And that's how we ended up with testing
21 different absolute doses.
22 But here, you can see that when plotted in

1 this way, that all three of the drugs produce dose-
2 related decreases in pupil diameter and decreases,
3 which are modest but significant in respiratory
4 rate, which is the measure that we're using here
5 for respiratory depression.
6 The format is similar to the last slide.
7 These are actually data from a composite scale, and
8 this is a scale that has many items that the
9 subject or the observer may check off a score on
10 whether or not they're endorsing that effect. This
11 is an opioid agonist scale, and so they're a number
12 of items that are typical of opioid effects such as
13 nodding, nausea, a tingling feeling, things like
14 that. So there's about 20 items on this scale.
15 And you can see that all three drugs
16 similarly increased ratings by the subject on the
17 agonist scale, and also, the observers provided
18 increased ratings of signs of opioid intoxication
19 that were dose dependent for all three drugs.
20 With regard to the relative potency
21 estimates, we took the variables for which we found
22 statistically significant findings and then

1 assessed whether or not they met the criteria for
2 conducting a valid bioassay according to Finney's
3 procedure.
4 When all of that was done, we were able to
5 determine that across measures, the potency
6 estimate for oxycodone and hydrocodone was
7 .93 milligrams to 1 milligram. And essentially,
8 what that mean is that hydrocodone is just a little
9 bit less equivalent. They're not 1 to 1 because it
10 takes 1 full milligram of hydrocodone to produce
11 the effects produced by .93 milligrams of
12 oxycodone, but they're very, very close.
13 These are data from the last study that I'm
14 going to present to you. This was also done in our
15 laboratory. And in this study, we examined the
16 effects of morphine, oxycodone and hydrocodone when
17 given intravenously to a cohort of prescription
18 opioid abusers. And in this case, we tested the
19 identical doses of each of the three drugs. So the
20 doses were zero, 5, 10 and 20 milligrams of
21 morphine, oxycodone and hydrocodone.
22 I just want to draw your attention to one

1 thing, and that is along the X axis, you're looking
2 at time. But each of those axes is broken because
3 the time frame from zero to 20 minutes after the
4 infusion is stretched, so that you can see the
5 immediate response to the intravenous infusion.
6 And then after the break, you can see that the
7 intervals between the time points are longer, and
8 that takes you out to six hours post drug
9 administration.
10 For all three drugs, you can see that the
11 onset of, in this case, liking for the drug and
12 other drug effects were immediately apparent within
13 minutes after the infusion and that they peaked
14 within generally the first 20 minutes of infusion,
15 as you would expect with rapid distribution, and
16 began to decline thereafter.
17 All three drugs produced generally dose-
18 related effects over this dose range, although the
19 two lower doses of morphine were more similar to
20 one another. And oxycodone at the highest dose
21 produced the greatest magnitude of effects with
22 there being some difference between oxycodone and

1 hydrocodone there.
2 Looking at peak outcomes for this study,
3 here the data are plotted for pupil diameter on the
4 left and expired end-tidal CO2 as our measure of
5 respiratory depression on the right. And you can
6 see that all three drugs significantly decreased
7 pupil diameter. Here it appears that oxycodone is
8 more potent at doing so compared to morphine and
9 hydrocodone. And all three drugs increased expired
10 end-tidal CO2.
11 This is the final figure from that data set.
12 This is looking at street values. The subjects are
13 asked to rate after they've experienced the drug
14 effect how much they would be willing to pay on the
15 street for what they received. And this allows us
16 to have some anchor against their own experience in
17 using illicit drugs. And you can see that all
18 three drugs produced dose-related increases in
19 estimates of street value with the highest doses
20 ranging of value between 30 and $40.
21 To summarize, from the studies that were
22 conducted in healthy volunteers without opioid

1 abuse histories, hydrocodone in combination with
2 homatropine or acetaminophen produces
3 dose-dependent eurphorigenic effects. These
4 effects are similar to those of morphine and
5 oxycodone. In these studies, hydrocodone at
6 20 milligrams looked approximately equivalent to
7 morphine at 40, and at 30 milligrams, approximately
8 equivalent to oxycodone at 20 milligrams.
9 Acetaminophen produced no discernible
10 effects alone, and in these studies, unpleasant
11 effects, including nausea and dizziness, occurred
12 at the upper end of the hydrocodone dose range as
13 does occur with other opioids in opioid-naive
14 individuals.
15 To summarize the findings from the studies
16 that were done in prescription opioid abusers,
17 hydrocodone produces dose-dependent increases on
18 ratings of positive subjective reports, including
19 ratings of liking, good effects, and endorsements
20 of street value. There's little to no evidence
21 that hydrocodone produces reports of negative or
22 unpleasant symptoms.

1 Hydrocodone is only slightly less potent
2 than oxycodone on a milligram to milligram basis on
3 subjective effects related to abuse potential. And
4 the profile of hydrocodone is similar to the
5 comparator opioids, including morphine,
6 hydromorphone, and oxycodone.
7 **Committee Questions to Presenter**
8 DR. J. WOODS: Thank you, Dr. Walsh.
9 Questions for Dr. Walsh? Let's see.
10 Dr. Suarez-Almazor.
11 DR. SUAREZ-ALMAZOR: Yes. Oxycodone and
12 acetaminophen combination drugs are classified as
13 Class II and hydrocodone and acetaminophen
14 combinations are classified as Class III. So I was
15 wondering if there are any physiologic,
16 psychological or behavioral differences that
17 justify this classification, in your view, this
18 differential classification.
19 DR. WALSH: That's the million-dollar
20 question, isn't it?
21 (Laughter.)
22 DR. WALSH: In fact, I think that they're

1 the same. That's what the bottom line -- I mean,
2 from a pharmacological perspective, the drugs are
3 the same. I think that there are other reasons why
4 there are scheduling differences, but I think that
5 if you look at just the single-entity products,
6 they are the same. I mean, someone might wonder
7 why aren't the oxycodone combination products in
8 Schedule III under the same conditions and are dose
9 restrictions on how much can be contained.
10 But I think based on all of the studies that
11 we have available to us, I think that there are
12 really very few, if any, pharmacological
13 differences.
14 DR. J. WOODS: Dr. Morrato.
15 DR. MORRATO: Thank you.
16 So building on that, I was most interested
17 in the data that you presented, though, in which we
18 had the marketed dose.
19 DR. WALSH: I'm sorry?
20 DR. MORRATO: In which we had the marketed
21 dose. I understand there's the intrinsic
22 pharmacological, as you're showing that. So if you

1 could bring up slide 10, I think, which is the
2 hydrocodone and acetaminophen. And I just want to
3 make sure I'm interpreting it correctly.
4 I mean, if you're looking at the 5-milligram
5 dose and you're comparing to the negative control
6 and the acetaminophen single active control, would
7 you say that they are similar, or would you say
8 that they're really different? So to support the
9 statement that at this marketed dose, there doesn't
10 seem to be sort of the benefit of acetaminophen on
11 reducing. I mean, what's been your experience?
12 DR. WALSH: Well, so as a scientist, I would
13 say that they're not statistically different, which
14 then kind of makes you say then they must be the
15 same. But these are small studies that have
16 limited power as well, so I think it's the dose-
17 related nature of it that gives us more
18 information.
19 But I mean, you're right. At what point
20 does it become an abuse-related problem? And of
21 course, if everyone took the drug as prescribed,
22 then we wouldn’t be here having a discussion

1 anyway. And of course, when people are abusing it
2 and it's being diverted, they're not taking
3 therapeutic doses, which is why we always test
4 super-therapeutic doses in these studies.
5 DR. MORRATO: That's what I thought. Thank
6 you for clarifying.
7 DR. JONES: I'd like to add something to
8 that, though, that I don't know that that's an
9 equivalent dose to morphine. So the morphine dose
10 is a higher -- if you're looking at a morphine
11 milligram equivalent basis, 40 milligrams of
12 morphine, it's not equivalent to 5 milligrams of
13 hydrocodone. So I don't think that's equivalent.
14 DR. WALSH: I don't think that was the
15 point. I think the question was about the
16 5-milligram dose.
17 DR. MORRATO: I didn't extend to the
18 positive effect on the other end. But, yes, I
19 would agree with you. I was looking at it from the
20 standpoint of the no effect but not -
21 DR. J. WOODS: Dr. Kaboli.
22 DR. KABOLI: Just a quick question on

1 commenting, if you're aware of other work that's
2 actually surveyed patients and people who abuse
3 thee drugs in terms of their preferences. I mean,
4 because what you're showing here seems like there's
5 similar effects. But out in the real world where
6 people are using these, what is the preference?
7 DR. WALSH: So that's a very good question.
8 Can I speak from personal experience rather than
9 from a data set?
10 DR. KABOLI: I'll give you permission to.
11 (Laughter.)
12 DR. WALSH: Dr. Woods?
13 With the population that we interact with,
14 the preference is for single-entity products. This
15 population grew up on OxyContin, and they're very
16 unhappy that it's no longer available in its
17 original formulation. And so we've seen a lot of
18 conversion to oxycodone because that's a
19 single-entity product that you can get a fairly
20 high dose formulation.
21 That being said, we see a tremendous amount
22 of hydrocodone abuse. One of the things in my

1 experience that differentiates them and I
2 think -- I don't know that there are really great
3 data on this. But the combination products are
4 generally not injected. So people know that there
5 are other components in it, and they try to steer
6 clear from injecting behavior, whereas we have a
7 cohort of prescription drug users in Appalachia,
8 that my colleague Jennifer Havens has been
9 following now for five years, of 500 abusers, and
10 about half of those people are injecting. And they
11 don't inject the combination products, hydrocodone
12 or oxycodone combination products by and large.
13 DR. KABOLI: Thank you. I was just going to
14 comment that if you do -- on Google, if you just do
15 a search and say which is a better high and you
16 don't do anything else, the first thing that comes
17 up is oxycodone or hydrocodone. And then there's
18 2.6 million hits and numerous forums discussing the
19 pros and cons where they can share. And it's
20 really fascinating that it's an ongoing debate
21 online.
22 DR. J. WOODS: Dr. Mendelson.

1 DR. MENDELSON: Yes. So, Sharon, on your
2 slide 17, pharmacologic class may be similar, but
3 you do show some dose response data here. And I'm
4 surprised that they weren't significant for
5 hydrocodone versus oxycodone and morphine.
6 Do you think that's because of the small N
7 in your studies, and what N might it have taken to
8 show a dose dependent difference here? It looks
9 like 5 milligrams of hydrocodone is considerably
10 less than using the famous eyeball test, which has
11 Type 1 and Type 2 errors associated with it. It
12 does look like the number is lower or the quantity
13 of intoxication is lower for hydrocodone.
14 DR. WALSH: Right. I think maybe I need you
15 to restate what the question is. We did find dose-
16 response effects. That's not what the issue is. I
17 think -- are you asking about comparing one dose of
18 hydrocodone to another dose of oxycodone, for
19 example?
20 DR. MENDELSON: Yes, because part of the
21 question before this committee is the dose at which
22 we would -- the schedule -- the recommendation that

1 the FDA is coming up with is that lower doses of
2 hydrocodone would be more approvable or more
3 appropriate for Schedule III than for Schedule II.
4 And your data do seem to support that a little bit
5 here, at least, that the hydrocodone -- the smaller
6 dose of hydrocodone seem to be different than the
7 smaller doses of oxycodone and morphine.
8 Would you say that's a fair statement or not
9 based on this data?
10 DR. WALSH: I think, based on this data,
11 with the intravenous data, that is fair. I think
12 that with the oral data, the drugs look more
13 equivalent to one another. But still at -- but at
14 the very lowest doses, you probably wouldn't see
15 much of a signal. So there definitely seems -- and
16 I think the FDA has put this into their summary,
17 that there is some threshold below, which it
18 appears that it's not problematic and above, which
19 you get a clear signal.
20 DR. MENDELSON: Excellent. I think that
21 answers my point.
22 DR. J. WOODS: Okay. I'm going to deviate a

1 little bit from what we have on our agenda. Just
2 to tell you that what I'm going to do is let
3 everyone go on a break, but I'm not forgetting the
4 people that still have questions related to the FDA
5 presentation. We'll get back to them after we get
6 the DEA side of this and before lunch. So I
7 haven't forgotten you, and let's take a break.
8 (Whereupon, a recess was taken.)
9 DR. J. WOODS: So we're going to go ahead
10 with the DEA presentation by Joe Rannazzisi.
11 MR. RANNAZZISI: Perfect.
12 DR. J. WOODS: I hope.
13 **DEA Presentation - Joseph Rannazzisi**
14 MR. RANNAZZISI: Good morning. I want to
15 thank the committee for the opportunity to appear
16 today and discuss hydrocodone combination products
17 and their diversion and abuse.
18 Before I get started, just a little bit
19 about myself. I'm a career special agent. I've
20 been with DEA for a long time, since the mid '80s.
21 I'm on my ninth year of a three-year tour in
22 Washington, D.C. I basically supervise the Office

1 of Diversion Control. The Office of Diversion
2 Control is responsible for many things regarding
3 industry, quotas, regulations, and scheduling. And
4 we take all those tasks extremely seriously, but
5 scheduling is something that is very important to
6 us.
7 To get started, for this presentation today,
8 we're going to provide a background to the drug
9 scheduling process, but the good news is the drug
10 scheduling process was discussed this morning. In
11 fact, my slides are almost exactly the same as
12 FDA's slides. It was almost like we took them out
13 of each other's books, which is the CSA.
14 So we're going to skip going through the
15 background of the drug scheduling process, and
16 we're going to go to discussing hydrocodone
17 diversion, trafficking and abuse, and then provide
18 facts and identify fiction related to the
19 consequences of rescheduling.
20 We talked about the mission statement. We
21 prevent, detect and investigate diversion of
22 pharmaceutical controlled substances and listed

1 chemicals from legitimate channels. But we also
2 have to strike a balance because we have to ensure
3 that there's an adequate and uninterrupted supply
4 of controlled substances to meet legitimate
5 medical, commercial and scientific needs.
6 It's based on the closed system of
7 distribution, and everybody in that closed system
8 has a responsibility to prevent diversion. All of
9 these people on that slide are registrants, DEA
10 registrants. In fact, we have approximately
11 1.469 million registrants, about 1.149 million are
12 practitioners, so doctors, dentists, vets. Then we
13 have about a little over 200,000 mid-level
14 practitioners. Those are nurse practitioners,
15 physician's assistants. Then we have the retail
16 pharmacies and the hospital clinics. Together all
17 of them have a responsibility under the Act.
18 Now, the closed system of distribution has
19 several working components, one of which is
20 establishing schedules. And that's what we're
21 going to be talking about today because
22 establishing schedules is a very important part of

1 the closed system of distribution because a
2 schedule dictates what type of recordkeeping is
3 necessary. A schedule dictates what kind of
4 security is necessary, what type of quotas are
5 obtained, so all that is part of scheduling.
6 Now, we've talked about the procedures of
7 controlled substance. I'm not going to belabor
8 that issue, but I want to talk factors really
9 quick. And I think it's important to go over these
10 factors one more time because today, we'll be
11 talking about Factor 1, Factor 4 and Factor 5,
12 actual or relative potential for abuse, history or
13 current pattern of abuse and scope, duration and
14 significance of abuse.
15 I want to tell you that we are married to
16 these eight factors. When the Drug Enforcement
17 Administration looks to schedule a drug, we're
18 married to these eight factors. We don't look at
19 anything outside of the eight factors, and I think
20 that's important that you all know that. So if
21 it's not in these eight factors, it's not really
22 determinative to us about a control action.

1 Now, you've got to understand the dynamics
2 of Schedule III and Schedule II. So let's talk
3 about Schedule III very quickly. A Schedule III
4 substance, the drug or other substance has the
5 potential for abuse that's less than the drugs or
6 other substances in Schedule I or II. The drug or
7 other substance has a currently accepted medical
8 use in treatment in the United States, and abuse of
9 the drug or other substance may lead to moderate or
10 low physical dependence or high psychological
11 dependence.
12 A Schedule III drug can be written. It can
13 be orally communicated. It can be faxed. It's
14 real easy to get a Schedule III prescription.
15 Doctor calls a pharmacist. He says, "This is
16 Dr. Smith. Hey, I got Mrs. Jones here. I'm going
17 to give her hydrocodone 7.5s, one tablet every four
18 to six hours as needed for pain, number 100. Give
19 her four refills." The pharmacist immediately
20 reduces that to writing, and that's the
21 prescription, very simple process.
22 Schedule II is quite different.

1 Schedule II, the drug or other substance has a high
2 potential for abuse. The substance has a currently
3 accepted medical use in treatment, and the abuse of
4 the drug or other substance may lead to severe
5 psychological or physical dependence.
6 That's the key. For those drugs on
7 Schedule II, Congress decided to cut out a special
8 part of the statute to ensure that these controlled
9 substances, particularly the Schedule II
10 substances, have some controls that limit the
11 amount of drug that's available for diversion.
12 Well, how do they do that? Well, first of
13 all, you have to have a written prescription. Now,
14 in some cases, you can do an emergency oral
15 prescription, 72-hour supply, but for the most
16 part, it's got to be a written prescription. Now,
17 the doctor has the ability to write a series of
18 prescriptions that are dated on the same day with a
19 "do not fill date until," up to a 90-day supply.
20 It's not a refill. It's an original prescription,
21 but it acts somewhat like a refill, so you don't
22 have to go to the doctor every month to get that

1 drug.
2 Those are the dynamics of those two classes,
3 Schedule II and Schedule III. Now, there are some
4 other things, and we'll get into it later on the
5 presentation.
6 Abuse is not defined by the CSA, and you've
7 heard that at least twice or three times today.
8 What I'm going to talk to you about is this
9 legislative history that suggests the following in
10 determining whether a particular drug or substance
11 has the potential for abuse. And that's what we're
12 going to talk about, a potential for abuse, an A
13 and B, where I'm going to be targeting this
14 presentation today.
15 Individuals are taking the drug or other
16 substance in amounts sufficient to create a hazard
17 to their health, or to the safety of other
18 individuals of the community, or there's a
19 significant diversion of the drug or other
20 substance from legitimate channels.
21 I think I could make a pretty darn good case
22 that this drug is being diverted, and I'm going to

1 tell you, I'm not going to talk about denominators.
2 I'm not going to talk about denominators. I'm not
3 a statistician. I'm not a PhD. I'm just a cop.
4 That's all I am, but I'm a cop with a lot of
5 practical knowledge because I don't care what the
6 denominators say, every day I deal in reality. And
7 the reality is abusers aren't taking one or two
8 tablets. Abusers are taking 10, 20, 30, 40
9 tablets. I had an ASIP doctor tell me he was
10 detoxing a patient that was taking 80 tablets a
11 day. Okay? It's not one or two tablets.
12 We all know that you build a tolerance to
13 the opiates. And the reason they're not taking one
14 or two tablets -- they might start that way, but by
15 the end of the day -- by the end the year, they're
16 taking a heck of a lot more than one or two tablets
17 because they need more to get that euphoria. They
18 need more to get that high, to get that
19 pharmacologic effect they're looking for.
20 So let's stop talking about, well, it's
21 based on one or two tablets. It's not. We're
22 talking about abusers here. These people are not

1 looking to get the desired pharmacologic effect,
2 that is, pain control. They're looking to get
3 high.
4 Standard distribution, it's the most widely
5 prescribed drug in the United States. Hydrocodone
6 and acetaminophen, the most widely prescribed drug
7 in the United States. You know the number. It's
8 over 130,000 or so prescriptions. The next closest
9 drug, simvastatin followed by lisinopril,
10 levothyroxine. We have an insatiable appetite for
11 this combination drug.
12 If you look, there's the top U.S.
13 pharmaceutical products dispensed by prescriptions.
14 There's hydrocodone acetaminophen right up there,
15 number 1. U.S. dispensed prescriptions total Rx's
16 in millions. I put up this slide to show you, look
17 at the hydrocodone and acetaminophen, and then look
18 at the oxycodone and acetaminophen, and then look
19 at hydrocodone and all, and oxycodone and all. You
20 can see there's a heck of a lot more prescriptions
21 out there on the street. Yes, there is. And
22 people are saying well, that's why you see more

1 drugs out there, and that's probably skewed because
2 there's so many prescriptions out there.
3 There's a reason there are prescriptions out
4 there. It's because the medical community, in my
5 humble opinion, is not taking this drug seriously.
6 It's in Schedule III. And I'm going to show you in
7 a little while how they're recruiting doctors on
8 the Internet scheme that they were doing back in
9 the mid and late 2004 to 2007.
10 State rankings, here's something
11 interesting. These are doctors that purchase
12 hydrocodone to be dispensed from their offices.
13 Now, check this out. The number one state is
14 California. Together, all those practitioners
15 purchased for distribution about 26 million tablets
16 in 2011. The next closest state was Georgia at
17 3.6 million.
18 Incidentally, if you don't know this -- I'm
19 pretty sure there are some doctors from
20 California -- California has got one of the
21 toughest hydrocodone problems in the United States
22 today, besides Texas and Tennessee and Kentucky and

1 some of those southern states.
2 Here's January 1st to September 30th, 2012.
3 Again, practitioner purchases, these are doctors
4 that are purchasing for distribution. Again,
5 they're in the 23-million-tablet range up until
6 September of this year.
7 Here are the pharmacies.
8 California -- these are purchases from January 1 to
9 September 30th, 2012 -- California, 752 million
10 tablets going to pharmacies, purchased by
11 pharmacies up to September 30th of this year,
12 followed by Texas. California and Texas, the top
13 two states that have hydrocodone acetaminophen
14 abuse problems.
15 Comparisons of hydrocodone sales to
16 pharmacies, if you look at this, there's -- this is
17 2010. This is the average, what the average
18 pharmacy in these states purchased. Well, in the
19 state of California, about 158,000 tablets in 2010.
20 Now, that middle state is New York at 60,093, and
21 then you have Texas at 161,000. And there is the
22 U.S. average at 121,000.

1 It's interesting to note that the other
2 states that are not on there -- and we just picked
3 the top three states by population. Here's a state
4 figure would be something like Kentucky. The
5 average pharmacy in Kentucky in 2010 purchased
6 about 220,000 tablets. In Tennessee, the average
7 pharmacy purchased about 284,000 tablets.
8 So what we're doing is we're seeing states
9 that have a very, very severe hydrocodone
10 acetaminophen problem, and they're consuming a lot
11 of hydrocodone. It goes to availability.
12 Let's talk about methods of abuse. Now, I
13 know my colleagues at FDA talked about the Drug
14 Abuse Warning Network and also Florida Department
15 of Law Enforcement and the American Association of
16 Poison Control Centers. I'm not going to belabor
17 that issue. We have a difference of opinion, just
18 like we have a difference of opinion on the
19 denominator. I'm not here to argue that. But just
20 be aware -- that's why it's in the
21 presentation -- that we believe the numbers support
22 what's going on as far as the abuse of these drugs.

1 But what we didn't talk about is this,
2 because this is a phenomena that's going on. This
3 is not manufactured by DEA or law enforcement.
4 This is happening, because hydrocodone is truly not
5 abused by taking a couple of tablets. Generally,
6 it's abused because they're taking it with a
7 potentiator.
8 What's a potentiator? It could be Flexeril,
9 carisoprodol, any of the other muscle relaxants.
10 They also take it with a benzodiazepine,
11 clonazepam, diazepam, or my favorite, alprazolam.
12 They use those together, and that's called the
13 trinity.
14 Now, if there are friends from the addiction
15 practitioners in the audience who've come across
16 this, they will tell you that a lot of young adults
17 are drawn to this combination. It is the
18 combination. They call this the trinity.
19 Actually, if you substitute oxycodone for the
20 hydro, that becomes the holy trinity. Okay? The
21 fact is that's a pattern of abuse, and we're seeing
22 it regularly.

1 If you're from Texas, I think Texas just did
2 a study within the last year and a half that showed
3 this combination is causing overdoses. This
4 combination, really, I don't see any pharmacologic
5 benefit to this combination of drugs. Yet during
6 the Internet crisis and now with these rogue pain
7 clinics, this is the combination at its best.
8 Now, you're going to say well, Rannazzisi's
9 a cop, right? What does he know about the
10 pharmacologic effect? Well, I'm also a pharmacist,
11 and I think I have a pretty good basis of knowledge
12 to tell you that there's no reason for this
13 combination and definitely not for every patient
14 that walks out of your clinic.
15 Opiates versus heroin, this is another one.
16 I can't get people to understand that this is not a
17 manufactured thing. This is happening, and it's
18 happening every day. And this is how it starts.
19 It generally starts with hydrocodone. Kids go to a
20 party. They may take an alprazolam tablet, and
21 then somebody offers them an opiate like
22 hydrocodone, the combination hydrocodone. And they

1 like it because it does have a nice euphoric effect
2 to it. And pretty soon, they're taking one or two
3 or three tablets, and as their tolerance builds and
4 they need more, they move to an oxycodone product.
5 Why? Because in their mind, because it's a
6 Schedule II, because their friend says, "Well, this
7 is more potent," they take it.
8 And they might go to the Percocet or
9 Percodan or whatever, Tylox, but in the end,
10 they're going to still need more. So what they do
11 is they go to the single-entity IRs, or if they can
12 get it, an oxymorphone product like Opana or
13 OxyContin.
14 Now, I know we talked about people who
15 inject and people who -- I'm telling you what we're
16 seeing is a lot of oral use. Once OxyContin left
17 and reformulated, we saw a lot of people going back
18 to oral use of these IRs and the OxyContin product
19 using a potentiator and using a benzo. That's what
20 we're seeing.
21 But in the end, you can't afford to do six
22 or seven IRs a day or five IRs a day. Why?

1 Because we're talking about between 30 and $80 a
2 tablet now. So what are they doing? They're
3 banging 10-dollar bags of heroin. And if you don't
4 believe me, go to your local addiction specialist
5 and ask them. Ask them who they're seeing now
6 that's on heroin. And they're going to tell you
7 kids. And they're going to say, "Well, where did
8 they start from?" because people don't generally
9 just say one day, I think I'm going to have some
10 heroin. They have to start somewhere, and they're
11 starting at hydro.
12 The next thing you know, we're losing a
13 generation. Why? Because they started on drugs
14 like hydrocodone. And this is going on. It's
15 going on everywhere. "Heroin Use Spikes in Area
16 Suburbs," this is the Examiner in Washington, D.C.,
17 all related to pill use. And there's substance
18 abuse treatment admissions. I'm going to blow
19 through this real quick. There's a significant
20 diversion of the drug or other substance from
21 legitimate channels.
22 Well, prescription fraud has been around

1 forever. I'm going to tell you that hydrocodone
2 was a target of prescription fraud for years, for
3 years. And when we were dealing with just
4 prescription fraud, it was easy. It's changed now.
5 We have pharmacies and burglaries. Here's
6 hydrocodone, reported thefts. This is diversion.
7 Eight million tablets in 2011. 2012, we're up to
8 5.9 million tablets reported thefts. There's the
9 oxycodone comparisons. If you look, those reported
10 thefts; 2011, oxycodone was higher. It looks like
11 in 2010 and 2012, hydrocodone is going to take
12 oxycodone in reported thefts.
13 Violence, you want to talk about violence?
14 Medford, Long Island, this is a pharmacy. A guy
15 walks in. He's looking for hydrocodone. He
16 engages the pharmacist. He takes out a gun, shoots
17 and kills the pharmacist, the clerk, and two people
18 in the pharmacy. Four dead, to get 10,000
19 hydrocodone tablets. It's not a diversion issue or
20 an abuse issue, or is it?
21 Diversion via the Internet. I know most of
22 you know about this, but we're going to go through

1 it real quick. Way back when, there was a group of
2 practitioners and pharmacists that just decided
3 they weren't going to follow the law. Doctors were
4 prescribing Schedule III, IV and V controlled
5 substances led by hydrocodone without seeing the
6 patient, without talking to the patient, based on a
7 questionnaire.
8 You get into the Internet and say
9 hydrocodone without a prescription, and a million
10 hits came up. You just pick one. You hit a
11 website. You fill out a questionnaire. The
12 questionnaire goes to a doctor. The doctor doesn't
13 even talk to you and issues you a prescription for
14 hydrocodone. It goes back to the website. The
15 website sends it to a pharmacy who never saw the
16 patient. And he fills the script and sends it out
17 to the patient. Within 72 hours, everybody gets
18 paid. The patient never saw a doctor. The
19 pharmacist doesn't know the doctor nor the patient,
20 but everybody was happy because those weren't real
21 patients, they were drug seekers. Because real
22 patients won't pay $300 for a hydrocodone

1 prescription for 100 tablets.
2 This is a scam. This is pure diversion.
3 You want to know how much diversion? How about
4 this? These are 34 pharmacies that we targeted in
5 one case, 34 pharmacies, that all they did was
6 facilitate Internet distribution. They
7 distributed, 34 pharmacies, about 98 million
8 tablets. But that's not diversion. And it's not
9 going to drug seekers who are abusing it. That's a
10 reality. This is reality. This drug has got a
11 hold of this society, and it's just killing us.
12 This is NFLIS. Now, real quick about NFLIS,
13 the National Forensic Lab Information System, about
14 80 percent of the labs in the United States belong
15 to this. Now, we're going to talk about two
16 things -- the state and local and federal labs.
17 We're going to talk about two things. There's
18 reports. That's a report of an actual drug that's
19 been submitted for analysis, and then there's
20 cases.
21 Now, you always have more reports than cases
22 because you might have one case where six reports

1 were submitted under it because it was a long-term
2 investigation. You might have one case where only
3 one report -- it was an arrest, a buy-bust arrest.
4 But in either case, it's a controlled substance
5 because it went to analysis and it was analyzed as
6 such. The particular drug that they expected to
7 find was what the lab found.
8 Now, if you look at this, which is
9 methadone, oxycodone, hydrocodone, you might be
10 wondering all the way up to 2009, hydrocodone had
11 taken oxycodone as far as the number of cases. And
12 indeed it did because all of our cases regarding
13 diversion, both state and local cases, were looking
14 at the Internet. And the primary drug that was
15 coming off the Internet was hydrocodone. It wasn't
16 oxycodone.
17 What happened in 2008 that kind of switched
18 this around? Well, Congress passed the Ryan-Haight
19 Act. And what did the Ryan-Haight Act do? It
20 totally shut down the Internet pharmacies, just
21 obliterated Internet pharmacies, because you had to
22 do an in-person visit. You had to tell the world

1 on the Internet who you are and who's facilitating
2 the prescribing on that site. And you got to have
3 a modified registration. And if you didn't have
4 that, you were going to jail, as simple as that.
5 So what did they do? They immediately
6 switched their business model, and they all became
7 pain clinics. And that's what happened. And I'm
8 not making that up. In 2006, there were four pain
9 clinics in Broward County. In 2007, there was like
10 20. In 2008, there was 66. In 2009, there was
11 142. Did a bunch of sick people just move down to
12 Broward County overnight? No, all those pain
13 clinics were basically Internet pharmacies that got
14 converted over. It changed. They changed their
15 business model.
16 NFLIS drug cases, look at this. This is
17 state and local forensic labs. If you look,
18 there's the hydrocodone. These are all Schedule II
19 drugs. Well, the codeine's mixed because you have
20 codeine single entity in Schedule II and then you
21 have the Tylenol II, III and IV. So let's just say
22 for the most part that codeine's mixed, but

1 meperidine, morphine, and methadone, all
2 Schedule II drugs, look at the number of cases.
3 Basically, one in two currently is
4 hydro -- or is oxy and hydro, back to back. All
5 those other Schedule IIs, is it because we're not
6 looking for those cases? No. It's because the
7 cases that we're getting for abuse and diversion
8 are hydro and oxy, back to back. That's a reality.
9 Rogue pain clinics, these clinics are just
10 nothing more than prescription dispensing mills.
11 And I know what somebody's going to say. Well, is
12 there something we could do to prevent this? No,
13 because if you're going to just write prescriptions
14 not for legitimate medical purpose and outside the
15 usual course of professional practice, which is
16 what U.S. v. Moore gave us in 1975, if you're going
17 to do that, it doesn't matter if it's a Schedule
18 III or Schedule II. You're just going to do it
19 because you're doing it because you're greedy.
20 Because when you operate a pain clinic, you're
21 driven by greed because you're making a lot of
22 money.

1 This is a pain clinic, lined up early in the
2 morning, get their meds. What's the drugs
3 prescribed? Hydrocodone and oxycodone. If you're
4 in Texas or California, your pain clinics are going
5 to do hydro. If you're in Florida, your pain
6 clinics are going to do oxy. If you're in
7 Tennessee, Kentucky, Missouri, it's a mixed bag
8 with hydrocodone taking the edge over oxy.
9 You want to talk about an investigation? I
10 could come out with hundreds of investigations, but
11 I'll just give you one. May 2011, this is
12 important. This is a pain clinic doctor. This
13 guy's name is Dr. Volkman. He used to travel down
14 from Illinois to a little town of Portsmouth, Ohio
15 to operate three pain clinics. He was dispensing
16 hydro, oxy, and some other drugs. And you know
17 what? He was killing his patients. He killed four
18 actually that we actually prosecuted on. He's
19 doing four life sentences. But again, hydrocodone
20 was part of that mix.
21 Our diversion, just DEA cases, in 2012,
22 we're doing 464 hydrocodone cases, and that's just

1 us. That's not the state and locals.
2 Again, here's all of the Schedule II
3 controlled substances looking at NFLIS. These are
4 local, state and federal labs. These are the
5 number of cases. Every one of those drugs, with
6 the exception of codeine which is mixed, is a
7 Schedule II.
8 The fact is that the two drugs that mean the
9 most, the two drugs that everybody are going after
10 are oxy and hydro. Yet we're treating them totally
11 different. Oxy's a Schedule II. Hydro's a
12 Schedule III. I'm telling you, when they were
13 recruiting the doctors for the Internet pharmacies
14 and the pain clinics, what they're saying is, look,
15 this is a Schedule III, IV and V drug that you're
16 prescribing. It's not the real bad stuff. I'm
17 here to tell you, hydro is the real bad stuff.
18 It's not a drug to be played with.
19 Obviously, you see that we sent the
20 recommendation back asking for reconsideration. I
21 had my staff do that because I believe this drug's
22 misclassified. I believe this drug's

1 misclassified, and I believe that by definition, if
2 you take all those factors, just the eight factors,
3 and what the definition of a Schedule II is as
4 related to Schedule III, that drug is
5 misclassified. And it's a fiction if we keep it in
6 Schedule III.
7 These are the questions I get from the Hill.
8 Hydrocodone combination products are less
9 susceptible to abuse because they have an
10 additional agent such as acetaminophen, aspirin,
11 ibuprofen or homatropine. That's bunk. That's
12 just not true. I don't care what anybody says.
13 Again, we deal with reality. We pick people up
14 that are taking 20, 30, 40 tablets a day. It
15 doesn't matter if --
16 You know what? If you're taking 40 tablets
17 a day for over three, four or five months, don't
18 you think you should have some type of liver
19 toxicity? We're talking to MEs. We're talking to
20 emergency room docs. We're talking to addiction
21 specialists. They're saying we're not seeing the
22 liver toxicity, and we know these people are taking

1 that quantity.
2 Hydrocodone products would be harder to
3 obtain to treat pain if it's placed in Schedule II.
4 Why? Look at all the oxycodone out on the street.
5 Seriously, why is it going to be harder to obtain?
6 You already can do the series of prescriptions in
7 Schedule II to get enough drug for every three-
8 month supply. And they're going to say, well, it
9 should be a six-month supply.
10 Really? A drug like hydrocodone, don't you
11 think you might want to have a little more medical
12 oversight than six months? Don't you think you
13 might want to go three months? Is it that bad that
14 you just can't see your patient every three months?
15 Burdens to pharmacies will increase purchase
16 of larger safes, higher overhead costs, more
17 paperwork. You don't have to have a safe in a
18 pharmacy. There's no federal law that requires a
19 safe in a pharmacy. In fact, 99 percent of the
20 pharmacies disperse their medication at the retail
21 level among all inventory. That's the way they
22 operate. You don't need safes. Now, manufacturers

1 need safes, but manufacturers also have -- they
2 probably have safes. They probably have large
3 safes because they're taking that bulk hydrocodone
4 in that's in Schedule II.
5 More paperwork? There is no more paperwork.
6 Paperwork is the same. In fact, it might be easier
7 if you use CSOS, the controlled substance ordering
8 system, to purchase the drug and if the doctors and
9 the pharmacies start doing electronic prescribing.
10 Then you don't have to worry about the separate
11 files. But for the most part, it's not a lot more
12 paperwork; in fact, very minimal paperwork increase
13 when it comes to Schedule IIs.
14 But this is my favorite. Patient care will
15 suffer, have to see a practitioner every month. I
16 think we talked about that. But this is my
17 favorite. Practitioners may not prescribe
18 hydrocodone if it's placed in Schedule II.
19 Listen, when a practitioner prescribes a
20 medication, the last thing on his mind should be
21 whether it's a Schedule II or III. When you
22 prescribe a medication for a patient, it's because

1 you made a medical determination that that patient
2 needs that specific drug. It has nothing to do
3 with the schedule. And if it does, then you've got
4 to really start thinking about how you're
5 prescribing. A prescription is prescribed to take
6 care of a particular ailment, and you've made that
7 determination that that drug is necessary to help
8 your patient. That's the process.
9 It goes back to this, and this is what I'm
10 concluding with, Schedule II or Schedule III. I
11 think it's obvious that the two agencies have a
12 disagreement, but once again, they don't have the
13 luxury of seeing what I see, or what my staff sees,
14 or every police officer that's working in narcotics
15 and pharmaceuticals sees every day. And we're
16 happy to take some questions.
17 **Committee Questions to Presenter**
18 DR. J. WOODS: Thank you.
19 MS. PHILLIPS: You mentioned electronic
20 prescribing, and that obviously would be more
21 auditable, safer, and less subject to diversion.
22 But currently, electronic prescribing is not

1 allowed for Schedule II. How close is the DEA to
2 allowing electronic transcription of prescriptions
3 for C-IIs?
4 MR. RANNAZZISI: Electronic prescribing is
5 allowed for C-IIs, IIIs, IVs and Vs. I'm right,
6 right? John?
7 JOHN: Not in C-III, no.
8 MR. RANNAZZISI: I'm correct. Look, there's
9 an interim rule out. I know I'm -- I'm not always
10 right, but I'm --
11 MS. PHILLIPS: There is an interim --
12 MR. RANNAZZISI: -- never wrong.
13 MS. PHILLIPS: There's an interim rule that
14 allows it, but there's no systems that have been --
15 MR. RANNAZZISI: There's an interim rule out
16 right now. The interim rule allows you to use
17 electronic prescribing. The interim rule kind of
18 sets up -- and there are people out there who are
19 electronically prescribing all controlled
20 substances. No?
21 John -- John, am I correct?
22 JOHN: I believe you're correct, sir.

1 MS. PHILLIPS: My understanding is there
2 have been no systems actually approved. They have
3 not implemented the regulations. There have been
4 no systems actually approved to do that in
5 practice.
6 MR. RANNAZZISI: Actually, if you go in the
7 last year, we've not only -- we don't approve
8 systems, but we do approve validations, companies
9 that validate or audit systems. And what the
10 systems do, the hardware and software systems
11 engineers do is go to these validation companies
12 and say, here's our system; would you validate it?
13 They look at the system. They determine if there's
14 any potential for diversion, if there's any
15 potential for breaching. And they give you a
16 statement that says this system meets the criteria
17 of the Code of Federal Regulations, Title 21, and
18 then you could operate.
19 I know there are people operating. I know
20 there are companies. I know that there are
21 practitioners that are operating.
22 It's an interim rule. There will be a final rule,

1 but like everything else with technology, we're
2 kind of moving in baby steps here because we want
3 to see that the systems out there are not prone to
4 massive breach. That's why we're using these
5 validation companies to look at the systems.
6 They're basically helping us identify potential
7 security violations or potential security areas
8 that could be breached.
9 MS. PHILLIPS: A follow-up question is, is
10 the DEA looking to eliminating the use of even
11 handwritten prescriptions once those electronic
12 systems are widely available?
13 MR. RANNAZZISI: That's a fantastic
14 question, and the answer is no. The statute only
15 authorizes us to create the systems. It doesn't
16 authorize us to take away.
17 Remember, the ability to write a
18 prescription is based on statute. Only Congress
19 could say no more, you have to do it by electronic
20 prescribing. We have no authority by regulation to
21 do that. I think it's in 829, I believe.
22 DR. J. WOODS: Dr. Landis.

1 DR. LANDIS: Just a couple of points of
2 clarification. You mentioned earlier that the DEA
3 now allows for three prescriptions for Schedule II
4 for 90 days, so those three scripts is a total of
5 90 days as long as they all have the original date
6 and then the date of dispensing; is that correct?
7 MR. RANNAZZISI: They have the original date
8 with a do not fill date, so you would have a 30-day
9 do not fill date, so, yes.
10 DR. LANDIS: What percentage of physicians
11 are actually utilizing that as this point?
12 MR. RANNAZZISI: I couldn't tell you.
13 DR. LANDIS: I would think the data would be
14 there because the scripts would be all dated the
15 same originally even though it's dispensed on
16 different dates.
17 MR. RANNAZZISI: The best people to tell you
18 that would be your local prescription drug
19 monitoring program. Remember, DEA does not
20 maintain a file of all prescriptions. We don't
21 have that type of database. The prescription drug
22 monitoring programs were tailored to fit the

1 specific needs of each individual state that has
2 one. Forty-nine states currently have a program in
3 place or one legislatively on the books that
4 they're working towards putting up. Only Missouri
5 has no prescription drug monitoring program.
6 But that information could be obtained from
7 the prescription drug monitoring program. We don't
8 look down at that patient level.
9 DR. LANDIS: Okay. Just to add on to that,
10 so can a physician then write one prescription for
11 a 90-day supply and still be within the rights of
12 it rather than three separate ones, for a
13 Schedule II?
14 MR. RANNAZZISI: What I could say is this.
15 There is no federal statute that dictates quantity
16 on a Schedule II prescription. I can't tell you
17 what you write quantity-wise, but remember, the
18 basis is the prescription has to be written for a
19 legitimate medical purpose in the usual course of
20 professional practice. That's basically the
21 standard. There is no quantity.
22 I know that's another thing that was kicked

1 around; well, there's a quantity limit. There is
2 no quantity limit in Schedule IIs.
3 DR. LANDIS: So any amount could be written
4 for one prescription. So they could still write
5 six months basically if it became a Schedule II; is
6 that correct, in one fill?
7 MR. RANNAZZISI: If they're doing it for a
8 legitimate medical purpose in the usual course of
9 professional practice -- and when doctors ask me
10 that question, I say, your medical records should
11 show exactly what you're doing. Your patient
12 records should say the reason I'm doing this is
13 because the patient, blah, blah, blah, and lay it
14 out, just to protect yourself. The best way to
15 protect yourself from legal action is to make sure
16 your medical records are intact and they're
17 complete.
18 DR. LANDIS: And also, real quick, on
19 electronic prescribing, which you're saying is out
20 there in the future, how many states actually do
21 not have anything on the book that allows for
22 electronic prescribing at this point?

1 MR. RANNAZZISI: I should know that. That,
2 I just don't know, but I could find out. That's
3 something I could find out and pass along to the
4 FDA.
5 DR. LANDIS: Thank you.
6 DR. J. WOODS: Dr. Kaboli.
7 DR. KABOLI: Just a real quick one, just in
8 clarification from the Controlled Substances Act,
9 who makes the initial determination of which
10 schedule -- say a new drug was coming out, does the
11 DEA do that or the FDA?
12 MR. RANNAZZISI: On a new drug, a brand-new
13 drug?
14 DR. KABOLI: Correct.
15 MR. RANNAZZISI: FDA sends a recommendation
16 over to DEA on a brand-new drug that hasn't been
17 scheduled yet. We look at it, and then our
18 scientists -- think of two set of scientists. We
19 have PhDs. FDA's got PhDs. They all look at the
20 same data, and generally, 99 percent of the time,
21 we agree. And once there's a meeting of the minds
22 and we all agree, we send it through the Federal

1 Register process, through the administrative
2 process, notice of proposed scheduling, and then a
3 final scheduling action.
4 DR. KABOLI: Thank you.
5 DR. J. WOODS: Dr. Suarez?
6 DR. SUAREZ-ALMAZOR: Yes. Most of the data
7 that you showed related to the abuse and the number
8 of cases and so forth showed an increase for both
9 hydrocodone and oxycodone. And in fact, the last
10 couple of years showed more of a problem with
11 oxycodone than hydrocodone, and oxycodone is a
12 Schedule II. So I was wondering if you could be a
13 little bit more specific as to why you think that
14 moving hydrocodone to a Schedule II would be
15 helpful. As you said, the bad guys will continue
16 to prescribe narcotics that are not indicated
17 medically in pain clinics and so forth.
18 So if we are seeing an increase in
19 oxycodone, how moving hydrocodone to a Schedule II
20 would help this problem?
21 MR. RANNAZZISI: Well, I believe that in
22 Schedule II -- and you're right. But the problem

1 with oxycodone is we're seeing a very specific type
2 of diversion where the practitioners that are
3 prescribing the drug really are not practicing
4 medicine for the most part. These are rogue pain
5 clinics. They're operating like drug dealers.
6 They're not operating like -- that's why you're
7 seeing this increase. If we removed the vast
8 majority of these rogue pain clinics, I think the
9 amount of oxycodone prescriptions would be
10 normalized.
11 The reason we want to move it is, one, you
12 have an enhanced controls on that drug. You have
13 enhanced -- just enhanced controls, regulatory
14 controls, to keep that drug out of the hands of
15 people. You can't do the six refills. Plus it
16 requires the doctor to provide a little more
17 oversight. So you're going to have to talk to the
18 patient, see the patient, at least get the patient
19 another prescription for another three-month supply
20 rather than a six-month supply.
21 I believe that -- plus, to be honest with
22 you, a Schedule III drug and a Schedule II drug

1 have very different sentencing guidelines.
2 DR. SUAREZ-ALMAZOR: But you have that for
3 oxycodone already, and it's not happening.
4 MR. RANNAZZISI: That's right because the
5 specific problem -- it's kind of a two-edged sword.
6 So we don't do anything, and we continue the
7 nonsense that's going on with hydrocodone right
8 now, or we move it into Schedule II. You put
9 additional controls on the drug and additional
10 penalties for dealing the drug. And then if
11 there's still a problem, maybe we should go a
12 different route.
13 But I think those additional
14 controls -- first of all, you've got to understand.
15 It's not a question of what happens if we put it in
16 Schedule II or not. It's a question of the eight
17 factors that we have. We have eight factors.
18 We're married to those factors. We have a
19 definition for Schedule II and Schedule III. It's
20 as simple as that. I can't look at what might
21 happen. I don't deal in hypotheticals.
22 The fact is on rescheduling action, I have

1 to go to the eight-factor analysis, and then I have
2 to look at the definitions that are contained
3 within Schedule II and Schedule III. And that's
4 it. I can't do a hypothetical of what would happen
5 if. That's not part of the determination process.
6 DR. J. WOODS: Dr. Morrato.
7 DR. MORRATO: Thank you.
8 I agree with you 100 percent that this is a
9 national epidemic that we need to address, and I
10 appreciate the passion that's very obvious from
11 your discourse here. But I do have a couple of
12 questions, and it builds, I think, on where
13 Dr. Suarez was heading.
14 It sounds like from the talk that the main
15 problem is significant diversion of the drug, and
16 you highlight a number: doctor shopping,
17 burglaries, pharmacies and clinics. So I'm hoping
18 that you can help us understand how rescheduling
19 affects that problem and source of diversion and
20 distribution. I mean, you started to go down a
21 few, but I'm having a hard time making the linkage
22 between scheduling and these other illegitimate use

1 or prescribing. So that's one question.
2 Then I have a second related to if there's
3 evidence of other examples of rescheduling that
4 might inform us on this. So I know there is one
5 that was talked about in our briefing materials
6 from New York State. They did a triplicate program
7 for benzodiazepine, which did not reduce the
8 problematic use of those drugs. And I don't know
9 if there's any evidence with regard to the
10 ephedrine containing products, and, in essence,
11 rescheduling, making it behind pharmacy counters as
12 opposed to OTC on the methamphetamine problem.
13 MR. RANNAZZISI: Let's take the last first.
14 DR. MORRATO: Sure.
15 MR. RANNAZZISI: Obviously, there is a huge
16 difference when they scheduled pseudoephedrine in
17 Oregon and in Mississippi. In Oregon, clandestine
18 labs went down 96 percent when they put
19 pseudoephedrine and ephedrine behind the counter.
20 In Mississippi, it went down 76 percent. And it
21 wasn't behind the counter. It was Schedule III
22 prescription only.

1 DR. MORRATO: Right, in those states.
2 MR. RANNAZZISI: We always believed that
3 pseudoephedrine and ephedrine should be a
4 controlled substance. That's the only way we're
5 going to deal with that problem. You're right.
6 Putting it behind the counter doesn't help, but
7 we're not requiring a prescription. We're dealing
8 with a clerk who's going to sell pseudoephedrine by
9 just taking somebody's license and running it
10 through a reader. That's not good control.
11 In fact, in the state of Kentucky when
12 Kentucky went to the electronic monitoring program
13 that they're using, their clandestine labs went up.
14 It didn't go down. They went up quite a bit. They
15 went from like 300 to 600 within two years.
16 So behind the counter didn't help. Neither
17 did electronic prescribing. But when you look at
18 Oregon and look at Mississippi, both states made it
19 a Schedule III. Both states made it prescription
20 only. Their labs plummeted. Mississippi's got
21 labs because they're getting the pseudoephedrine
22 from the surrounding states. So in that case, yes,

1 control did its job. And if you use that as a
2 model, you're not going to have a methamphetamine
3 problem in the United States, based on clandestine
4 labs in the United States. You'll have a
5 methamphetamine problem, but it's going to be
6 coming from outside of the country.
7 DR. MORRATO: So that's evidence that would
8 be supportive of the impact of scheduling on the
9 larger problem.
10 How about -- are you familiar with the one
11 that was the New York State program that I think
12 was done in the late '80s.
13 MR. RANNAZZISI: The triplicate prescription
14 program? I'd have to -- the people I know in New
15 York State thought the triplicate prescription
16 program did work. It identified problems within
17 the prescribing community and the dispensing
18 community, and they were addressed.
19 Remember, New York State just made
20 hydrocodone a Schedule II in their new bill, and
21 they also, I believe, mandated prescription drug
22 monitoring program searches before they prescribe a

1 controlled substance. So New York State's moving
2 very quickly to handle their issue, their problem.
3 Should more states do it? The states have
4 to tailor what they need, but I think New York
5 State, after this last multiple shooting in that
6 pharmacy, decided enough is enough.
7 DR. MORRATO: So many places are taking very
8 multipronged, and it's hard to tease out the effect
9 of individual things.
10 I mean, I guess to my first question, how do
11 you see the linkage -- it seems -- how do you see
12 the linkage between scheduling and addressing
13 problems of doctor shopping, robberies, burglaries,
14 rogue Internet pharmacies and rogue pain clinics?
15 MR. RANNAZZISI: See, again, you're asking
16 me to answer a question. I could tell you, but
17 that's not part of the determination of whether a
18 drug should be scheduled or not. The determination
19 is based on the eight factors.
20 What could possibly occur because of a
21 rescheduling action is not part of the
22 determination process. So I could give you an

1 idea. I believe that the N controls will secure in
2 the supply chain, so it's not going to be diverted
3 easily. Remember, on the distribution or the
4 manufacturer level, they don't have to put it a
5 cage. Once it becomes Schedule II, they have to
6 vault it. They have to have minimal access to that
7 vault.
8 You're not going to see the six-month supply
9 out there. And I don't remember which speaker said
10 it, but he or she's absolutely right. A lot of the
11 drugs are getting into the medicine cabinet.
12 You're getting a 90-day supply and another three
13 refills after that, and it's going into the
14 medicine cabinet. And then the kids are seeing it
15 because the kids are listening to people who are
16 saying, hey, this is a great drug. It's better
17 than whatever, and they go in and take it. And
18 that's how the cycle of abuse begins.
19 DR. MORRATO: So do you anticipate that one
20 unintended consequence might be then I'm a doctor
21 that doesn't want to have to write three individual
22 prescriptions. I write it for my 90 days, and you

1 can fill up to that amount; that you'll actually
2 see larger prescriptions being written initially
3 that end up not being used and therefore, there's
4 more in the home cabinet?
5 MR. RANNAZZISI: Well, I think on that
6 series of prescriptions, a 90-day supply is much
7 better than a six-month supply because that's
8 what's happening right now. A lot of doctors are
9 writing scripts with five refills.
10 DR. MORRATO: But we saw evidence earlier
11 this morning that the median duration of use is
12 more like, I believe, 14 days. So I'm not arguing
13 that there aren't extremes and there is definite
14 abuse and that, but I'm trying to kind of wrap my
15 mind around what is the norm and what is the
16 extremes, and should the extremes be targeted in a
17 different manner. Because we have to weigh the
18 burden on to the system, on to patients. And I
19 think having clear evidence that justifies the
20 benefit of what you're doing helps people
21 understand why they're taking on more burden.
22 MR. RANNAZZISI: I'm not going to be able to

1 provide you clear evidence because there is no
2 clear evidence until the drug actually gets to that
3 schedule and we see what it's like in practice.
4 We're dealing with hypotheticals here. All I could
5 tell you, again, is when I look at a drug for
6 rescheduling, my determination is based on abuse
7 and then the scientific factors that HHS and FDA
8 look at regarding the pharmacology, public health
9 risks, and things like that.
10 DR. MORRATO: Thank you.
11 DR. J. WOODS: Thank you.
12 I'm going to put both the questioners and
13 the answerers in Schedule I, because they're
14 affecting my diet very badly.
15 (Laughter.)
16 DR. J. WOODS: So I want to ask all of you
17 to show some restraint so that we can have some
18 time for lunch.
19 Ms. Chambers.
20 MS. CHAMBERS: Thank you.
21 I do have two questions. I do agree with
22 you. We need to deal not with hypotheticals but

1 just what is. And I would like to know what have
2 you done to assess the impact on the patients
3 because I haven't heard any evidence presented
4 anywhere here today, especially by your department,
5 towards the FDA that has shown that there isn't
6 going to be an impact on patients.
7 Have you done patient surveys systematically
8 to understand what's happening in the communities?
9 I'm a patient advocacy organization. I hear the
10 stories. I know what's going on the patient ground
11 level with the restrictions that have already
12 happened, with what has been done with the DEA.
13 Yes, we need to get the pill mills off the street
14 and et cetera, but the patients are being
15 significantly impacted.
16 So my first question is, what have you done
17 to systematically find out what's happening to the
18 patients?
19 MR. RANNAZZISI: We haven't because the fact
20 is we don't believe that there's going to be an
21 issue with patients getting those drugs. Just
22 putting aside, look at Adderall and Ritalin and all

1 those ADHD drugs right now. They're all
2 Schedule II. Are there patients having a problem
3 getting those drugs?
4 MS. CHAMBERS: There's not the emotional
5 impact around those kind of drugs as there are this
6 chronic pain issue because that's not related to
7 the enforceability of illegal acts. There's
8 nothing concerned there.
9 You've put under here in your fact or
10 fiction, "Patient care will suffer. Patients will
11 have to see a practitioner every month." I know
12 that people on Medicaid, they don't have the gas to
13 get to the doctor who will see them. One of the
14 few physicians who will take a Medicaid patient,
15 they don't have the gas to get to that doctor every
16 month to get that prescription.
17 MR. RANNAZZISI: If the drug is placed in
18 Schedule II, we've made -- we have regulations in
19 place so the doctor doesn't have to see the patient
20 every month. He could prescribe a series of
21 prescriptions to ensure that that patient has a
22 90-day supply. It's not going to affect patient

1 care. The only effect that it's going to have on
2 patient care is he might have to see the patient
3 every 90 days rather than every six months.
4 MS. CHAMBERS: That may happen. I know that
5 right now the FDA has asked for opinions on the
6 concern with the opioid prescribing. That's not
7 what we're discussing here today, but I know where
8 this is headed. And it's to restrict the access of
9 these pain medications generally.
10 When you start putting this kind of chilling
11 effect on to our physicians who are treating the
12 patients, they don't want the hassle. They don't
13 have the time to see the patients to begin with who
14 are in chronic pain, and we're talking about 100
15 million Americans. It's not just a handful. They
16 don't have the time to spend with them to figure
17 out what -- how to see more patients.
18 With the Affordable Care Act increasing 30
19 million people on to the doctors who are available,
20 they've already made changes in having the nurse
21 practitioners -- excuse me -- not nurse
22 practitioners but the nurse anesthetists, they can

1 now treat chronic pain. They can diagnose, treat
2 and prescribe for those patients. And they are not
3 fully trained to be able to treat them like a
4 medical doctor.
5 Now, you're changing the setting because now
6 these patients aren't even receiving the full care
7 that they would have from a regular physician. And
8 so the doctors who would have seen those patients
9 are turning them away because they don't want to be
10 burdened with the chronic pain setting. And so I
11 am asking you, please, let's systematically survey
12 the patients to find out what's happening already
13 to you.
14 MR. RANNAZZISI: I understand, ma'am. I
15 understand what you're saying. However, the fact
16 is, is we do not believe that a three-month
17 supply -- a 90-day supply, as compared to original
18 script and five refills is that big of a
19 difference. And if you're a chronic pain patient,
20 don't you believe you should have a little more
21 oversight than every six months?
22 MS. CHAMBERS: I would love to think that

1 people could have more oversight than every six
2 months, but the fact is, is that the access to a
3 physician is so limited. It's not a -- we're
4 dealing with facts. I'm using your words of let's
5 deal with what is, not just hypotheticals. The
6 fact is, is people are having problems having
7 access to a physician.
8 MR. RANNAZZISI: The fact is, is that there
9 is so much hydrocodone on the street, it's getting
10 into the wrong hands. And reality is when I have
11 to speak to a parent who's lost a kid because he
12 overdosed because his friend gave him a potentiator
13 and hydrocodone and then drank some alcohol.
14 That's a reality, and it happens all the time. And
15 I'm sure that patient advocacy groups should talk
16 to the survivors of overdose victims' families, and
17 you guys could get together because they have a
18 whole different opinion. Because there's so much
19 hydrocodone out on the street right now, there's so
20 much hydrocodone because of the indiscriminate
21 prescribing practices of certain practitioners, and
22 it's got to stop.

1 We're giving you an out. There's a 90-day
2 supply. If you're a chronic pain patient, I don't
3 see what the problem is with getting oversight
4 every 90 days so a doctor can look at you and see
5 where you are, and see if he might be able to
6 adjust the medication accordingly to --
7 MS. CHAMBERS: But you aren't dealing
8 with --
9 DR. J. WOODS: Point's made, folks. Let's
10 call this one off.
11 Dr. Crawford.
12 DR. CRAWFORD: Thank you.
13 Administrator Rannazzisi, we appreciate your
14 presentation very much, and my question really was
15 the same as Dr. Suarez, so just to make sure I'm
16 understanding the responses right. Essentially,
17 because we were looking at the presentation for the
18 take home, one of the key messages at least was the
19 problem, from DEA's perspective, especially with
20 the abusers, oxycodone products and hydrocodone
21 products. And in answer, essentially, if I
22 understood correctly, when asked about how would

1 up-scheduling from C-III to C-II impact what's
2 going on, the answers I heard were enhanced
3 regulatory controls, more medical oversight,
4 different criminal consequences. But it still
5 would be a hypothetical until it happened as to
6 whether or not it would keep the hydrocodone
7 products from the wrong hands and prevent abuse.
8 Is that correct?
9 MR. RANNAZZISI: That's correct. And we
10 could keep it in Schedule III, and the problem
11 could just keep getting out of control, or we could
12 try something different.
13 DR. J. WOODS: Dr. Hernandez-Diaz.
14 DR. HERNANDEZ-DIAZ: Same question as
15 Dr. Suarez.
16 DR. J. WOODS: Dr. Nelson.
17 DR. NELSON: Thank you.
18 And maybe we can keep it brief, but one of
19 the problem is I have is there's some internal
20 inconsistency. And you guys at DEA are going to
21 have to decide and explain to us maybe how do you
22 determine -- I know there's nothing objective, but

1 how do you determine the abuse potential or the
2 high potential for abuse to make it Schedule II,
3 whereas less abusable than some unknown objective
4 standard to put it into Schedule III, it would seem
5 to me that we might be splitting hairs here because
6 we're hearing that the abuse potential between the
7 two is essentially the same, but yet one might have
8 a little bit more than the other which would knock
9 it down into Schedule III.
10 I mean, conceivably, if another drug came
11 out that was more abusable than oxycodone in
12 Schedule II, would it then knock oxycodone down
13 into Schedule III? And I don't mean to sound
14 facetious, but how do you determine this relative
15 abusability?
16 MR. RANNAZZISI: I guess let me ask you a
17 question. Do you think that morphine is more
18 abusable and more potential for abuse than
19 hydrocodone combination products?
20 DR. NELSON: Well, it's not what I think,
21 but --
22 MR. RANNAZZISI: No, I'm just asking you

1 because that's the question, because the question
2 is whether a Schedule III product has less
3 potential for abuse than the Schedule II products.
4 Now, you have several Schedule II
5 products -- hydromorphone; I believe that
6 hydromorphone -- and I think Dr. Walsh, based on
7 her information, I think it confirms that it's
8 similar if not greater potential abuse than
9 morphine. Morphine's been in Schedule II for a
10 long time, meperidine, Demerol --
11 DR. NELSON: The question that we're
12 ultimately being asked is, is hydrocodone more or
13 less or equal or less abusable than oxycodone, and
14 that's ultimately the question, right?
15 MR. RANNAZZISI: Well, if you're going by
16 diversion, just straight diversion, I think it's
17 equal to oxycodone.
18 DR. NELSON: But how do you then determine
19 which -- because there's no standard for
20 abusability. It's all going to be relative. So
21 somehow, we have to know what you consider
22 relatively less or more abusable.

1 MR. RANNAZZISI: If you go back to the slide
2 that -- Congress set out what they believed were
3 the determinators of what potential for abuse is,
4 and there were four factors on there. The last
5 factor, which we didn't even talk about, was actual
6 abuse. Actual abuse. And I think they said
7 something to the effect that, well, obviously, if
8 the drug is an actual abuse, its potential for
9 abuse is there.
10 But in the end, I concentrated this
11 presentation on diversion because diversion was one
12 of the factors that showed potential for abuse.
13 You don't divert a drug at a legitimate healthcare
14 delivery chain just because you're doing it as a
15 favor. You're doing it because the diversion is
16 due to someone in that chain wanting to abuse the
17 drug.
18 DR. J. WOODS: Dr. Woods.
19 DR. M. WOODS: My question originally was
20 similar to Dr. Crawford's and Dr. Suarez-Almazor's
21 and Dr. Morrato's. But I guess the struggle I am
22 having is given the sheer volume of hydrocodone

1 that's out there and the sheer volume of oxycodone
2 that's out there, in looking at the abuse data, I
3 am just struggling to see how rescheduling
4 hydrocodone's going to make a huge difference.
5 But I will make one other observation. In
6 one of your early slides, the top 5 prescription
7 drugs sold in the U.S., I think your point was look
8 at hydrocodone. But since the most common reason
9 people seek medical attention is for pain, I guess
10 I didn't find that particularly surprising and was
11 happy to see that the lipid-lowering agents were
12 equal to hydrocodone when you add those up.
13 But I guess the other thing that I've been
14 sitting here struggling with is the Controlled
15 Substances Act of 1970, and you've talked about the
16 differences in enforcement with the different
17 levels. But that's 42 years old, and I'm wondering
18 do we need to rethink that whole system. But that
19 would be a question for another day.
20 MR. RANNAZZISI: I don't think
21 any -- technology has bypassed the Controlled
22 Substances Act in some respects, but the Controlled

1 Substances Act, believe it or not, is a very fine
2 document. It built in certain things that are
3 adapting to the problems. Obviously, in 1970, no
4 one knew that technology was going to take us where
5 we are today.
6 But for the most part, the Controlled
7 Substances Act, Congress was extremely innovative
8 when they created the closed system of
9 distribution. If you look at what they did back in
10 '70, they were visionaries because they looked at
11 certain things and said we need to do this because
12 in the future, there may be a problem. They didn't
13 hit on every problem that we encounter, but for the
14 most part, the Controlled Substances Act is
15 adapting fairly well to what we're seeing today.
16 Not everything, but then again, it's an old
17 document.
18 Should it be changed? I'm sure
19 technologically -- Congress has got a lot on their
20 plate right now. The Controlled Substances Act,
21 while it's important, is probably taking a back
22 seat to some other things.

1 DR. J. WOODS: Okay. Thank you, Mr. DEA.
2 We're now going to break for lunch. I
3 haven't forgotten the questions that haven't been
4 answered. We'll reconvene again in this room in an
5 hour. It looks to me like that's going to be just
6 a little bit after 1:00. Let's cut it a little
7 short and reconvene at 1:00.
8 Panel members, remember that there should be
9 no discussion of the meeting during lunch amongst
10 yourselves or with any member of the audience.
11 Thank you for your attention.
12 (Whereupon, at 12:10 p.m., a luncheon recess
13 was taken.)
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1 A F T E R N O O N S E S S I O N

2 (1:03 p.m.)

3 DR. J. WOODS: For those of you who are

4 going to sit on the committee, please take your

5 seats, and we'll get started soon. We're going to

6 start this afternoon with an industry presentation.

7 Mr. Gaugh, please introduce yourself.

8 **Industry Presentation - David Gaugh**

9 MR. GAUGH: Thank you, Mr. Chairman.

10 Good afternoon, everyone, and thank you to

11 the committee and the FDA for allowing the Generic

12 Pharmaceutical Association to present at this very

13 important meeting. My name is David Gaugh, and I'm

14 senior vice president for sciences and regulatory

15 affairs at GPhA, and I'll be representing the

16 companies of GPhA.

17 Just a quick note of outline, so we'll go

18 through some introductions, a little postmarketing

19 data, which I know there's been a lot of data

20 presented today, so pretty consistent information

21 is coming across. Potential consequences with

22 rescheduling, some risk management alternatives,

1 then the generic drug company sponsors' proposal,
2 and finally our conclusions.
3 So first would be a disclaimer that I'll
4 provide, and the disclaimer is that GPhA members
5 are not experts, of course, in the complexity of
6 abuse and addiction deterrence and prevention.
7 Recognizing the complexity of this issue, GPhA does
8 not have the expertise to advocate for a particular
9 strategy.
10 We do claim that our evaluation is a
11 comprehensive analysis of the issues but represent
12 an assessment of factors that require further
13 evaluations with experts in the field. So
14 ultimately, my ask at the end of this will be, as
15 we move forward with this is to be able to continue
16 to collaborate as we work on this project.
17 From a GPhA perspective, we represent 30 of
18 the generic manufacturing companies. These would
19 be the companies that represent about 85 percent of
20 the generic drugs sold in the United States today,
21 which are also manufacturers of hydrocodone-
22 containing analgesics and cough products. What we

1 do not represent are brand pharma and also
2 manufacturers that are not in GPhA. So while we
3 represent 30 generic pharmaceutical companies,
4 there's about another 100 in the generic space that
5 we do not represent.
6 With that, let me go into some quick
7 introductions. So from a summary standpoint, GPhA
8 acknowledges that the rise in abuse and misuse of
9 hydrocodone containing products is an absolute
10 issue that's before us. And that said, there's no
11 evidence that a more restrictive schedule curtails
12 abuse or misuse of opioids and may simply shift the
13 abuse and misuse to other both licit and illicit
14 products.
15 When considering rescheduling hydrocodone-
16 containing products to Schedule II, there are other
17 factors that should also be considered: impact on
18 patient access to pain relief; impact on healthcare
19 systems; impact on pharmaceutical supply chain,
20 manufacturers, wholesalers and the retailers; and
21 finally, hydrocodone-containing products, if they
22 are reclassified as Schedule II, all links in the

1 pharmaceutical supply chain will need to be worked
2 together to establish that appropriate process.
3 So again, I come back to that collaboration.
4 If we go down this path, there are a lot of nuggets
5 in the chain, if you will, that we'll need to work
6 together to make sure this happens and happens
7 appropriately.
8 Use of hydrocodone-containing products.
9 Again, we've covered a lot of this already today,
10 so I'll go over it rather quickly. But
11 hydrocodone-containing products have two primary
12 uses, the symptomatic relief of moderate to
13 moderately severe pain and symptomatic relief of
14 nonproductive cough alone or in combination with
15 other antitussives and expectorants.
16 Hydrocodone-containing analgesics as a group
17 are the most prescribed pain medication in the U.S.
18 In 2008, that was 124 million doses, and I know we
19 saw some other numbers up here. In 2011, it's
20 risen to 131 million. So that volume of number of
21 prescriptions, number of pills, if you will,
22 dispensed is a very important factor to note when

1 we get into the abuse of products one versus
2 another.
3 Some postmarketing data, placement of drugs
4 in Schedule II, they do not necessarily reduce
5 abuse or misuse or diversion, which I know was
6 brought up before. So if we look at some
7 postmarketing data -- and this data again is very
8 similar to what we've seen already this morning.
9 But if you look at non-medical use per 100,000
10 population, despite significantly higher overall
11 use of hydrocodone-containing pain products, so the
12 actual quantities of products sold and used by
13 patients, rate of ED visits for the non-medical use
14 are similar or lower than the rates for oxycodone,
15 which is a Schedule II product. And this comes out
16 of the DEA ARCOS system, is where the database for
17 this comes from.
18 Additional information on postmarketing,
19 abuse among unique recipients of dispensed drugs.
20 In the total population, hydrocodone-containing
21 products have only a slightly higher rate of abuse
22 than oxycodone despite a significantly higher

1 utilization overall. Among unique recipients of
2 dispensed drugs, hydrocodone-containing products
3 have a lower rate of abuse when compared to both
4 Schedule II and Schedule III opioids. And this
5 again is coming out of the Denver program, which is
6 RADARS. And the charts are pretty explicit in
7 showing both of those factors from an abuse rate
8 potential.
9 Again, postmarketing data and rates of
10 diversion in the total population, hydrocodone-
11 containing products have a similar rate of
12 diversion as oxycodone despite significantly higher
13 utilization rates overall. And among unique
14 recipients of dispensed drugs, hydrocodone-
15 containing products have the lowest rate of
16 diversion among those opioids tracked.
17 So again, both of these charts are pretty
18 busy with all the products that are in there, and
19 hopefully, you can see those. Maybe not in the
20 back of the room, but hopefully, the committee can
21 see them. As you go down from buprenorphine at the
22 top to oxycodone at the bottom from a color chart,

1 that middle chart, you can see where each of these
2 fall. But hydromorphone is down at that lower
3 level, if you will.
4 So potential consequences of rescheduling
5 hydrocodone-containing products. And again, the
6 data that I just showed has been seen in two or
7 three presentations today, so I think it's all
8 pretty consistent data and why I went through it
9 rather quickly. So potential consequences of
10 reclassifying hydrocodone-containing products to
11 Schedule II may have significant impact on patients
12 who require pain relief, both acute, subacute, and
13 chronic.
14 And why is this? There are few prescribers
15 of Schedule II products in the healthcare system
16 that are actually allowed to prescribe these
17 products. So they have limited choices for both
18 moderate and moderately severe pain in that
19 Schedule III category. More than half the staff at
20 urgent care centers in today's environment are
21 nurse practitioners, physician's assistants, which
22 the DEA does not refer to as mid-level

1 practitioners and in many states cannot prescribe
2 Schedule II products.
3 As we're seeing more and more healthcare
4 systems downsizing, if you will -- and I know many
5 of you around the table know that to be a
6 fact -- we're going away, I guess if you will, from
7 the physicians being that primary first caregiver
8 to the physician's assistant and nurse
9 practitioners being able to do that, which is great
10 from a healthcare system perspective, great from a
11 patient perspective, but maybe not so from a
12 prescribing perspective.
13 Many dentists do not have a Schedule II
14 narcotic registration with the DEA and therefore
15 will be limited in the pain relief that they are
16 able to give their patients. And patients who
17 require hydrocodone-containing products for
18 management of their pain may be forced to seek care
19 outside their current networks of primary care
20 providers for access to physicians that can
21 prescribe Schedule II substances, thereby shifting
22 burden from the care of the lower cost providers to

1 a higher cost provider process.
2 Then finally, licensed pharmacists will bear
3 a heavier burden at the retail level to accommodate
4 the state regulations. So I realize that the DEA
5 has certain regulations of their own, but so do
6 states have additional regulations on top of that
7 for pharmacists only dispensing and their
8 accountability of the Schedule II products. So
9 pharmacists may have significantly less time to
10 devote to the patient care activities and the
11 patient care counseling that is so important and so
12 needed by that segment of the healthcare givers.
13 Potential consequences, again from a
14 pharmaceutical supply chain standpoint, significant
15 and costly changes to facilities and processes for
16 manufacturing, packaging, and distribution of
17 hydrocodone products. So again, that number of
18 131 million doses that are being dispensed is a
19 significant amount of product, and so it's going to
20 have to have a significant amount of storage. And
21 so while the API that comes in, the active
22 pharmaceutical ingredient that comes in that is a

1 Schedule II, then it goes into the actual product
2 and the bulk quantities of product and their
3 packaging, et cetera, now becomes a Schedule III.
4 If that moves to Schedule II, all of that storage
5 will have to be significantly increased by the
6 companies throughout the supply chain process, all
7 the way down to the pharmacists.
8 So larger vaults associated with security
9 systems to manufacturing, packaging and receipt and
10 storage, as I just mentioned, larger in-store
11 safes. While it is true some pharmacists and
12 pharmacies do not store in safes and are not
13 required to, most of them do because of the
14 significant issues with these products and the
15 thefts that are occurring. So they are locking
16 them up, and that would require a larger space for
17 that, and incremental staff pharmacist to directly
18 manage and account for these Schedule II products
19 that any other pharmacy, quote, "healthcare
20 provider" is not allowed to do.
21 From a risk management standpoint,
22 alternatives to limit abuse, rescheduling

1 hydrocodone products may not lead to a decrease in
2 abuse, misuse, or diversion of hydrocodone
3 products. And that's something that's been stated
4 before, and we will state it again. The
5 rescheduling only addresses the supply chain of the
6 abuse and the misuse.
7 Other supply chain controls such as
8 tamper-resistant prescription pads and requirements
9 for dispensing have not reduced the access. So
10 that's already been looked at, already been tried,
11 and has not made a significant impact. Some
12 impact, yes, but not significant.
13 Continued abuse and diversion of
14 prescription drugs from legitimate sources
15 demonstrates inadequate supply side approaches
16 alone. And then rescheduling of hydrocodone
17 products may shift abuse and misuse to more
18 accessible products.
19 Next would be the research from National
20 Institutes of Health. The National Institute for
21 Drug Abuse has consistently demonstrated that the
22 most effective approach to addressing the problem

1 of drug abuse, and includes balanced efforts
2 between supply and demand reduction. So
3 prescription drug abuse prevention and treatment
4 programs are crucial.
5 So this is not a one silver bullet process.
6 I think we all know that, and that's what we
7 believe is very important, is that we're not
8 looking at this for one silver bullet but what are
9 we going to do to go beyond that.
10 FDA, industry, and other stakeholders must
11 identify the appropriate balance of supply and
12 demand measures to ensure that medications remain
13 accessible to the patients who truly need them.
14 So our proposal from the generic drug
15 sponsors would be, one, to conduct additional
16 studies to specifically assess the abuse of
17 hydrocodone. That was asked around the table
18 earlier today, I know, and so we would echo that as
19 well.
20 Develop a balanced approach to reducing the
21 supply and the demand without having a negative
22 impact on the patient access.

1 Partner with all stakeholders, public and
2 private, to educate the appropriate use and safe
3 disposal of hydrocodone-containing products. So
4 there are a lot of things that are out there for us
5 to discuss and talk about. This is one of them,
6 absolutely.
7 Abuse deterrent, something that the FDA just
8 introduced on January 9th is another education of
9 the healthcare professionals we think is an
10 extremely important piece of this. So multiple
11 things that we need to look at and consider, not
12 just the one fact of changing it from Schedule III
13 to Schedule II.
14 If rescheduled, manufacturers request the
15 opportunity to work with wholesalers, retailers and
16 the regulatory agents to establish a process and
17 timeline that enables all stakeholders adequate
18 time to ensure uninterrupted patient access to
19 hydrocodone-containing products.
20 With that and my last slide, so for
21 conclusion, we absolutely agree that there is a
22 problem of prescription drug abuse in the United

1 States, and hydrocodone-containing products are one
2 of those that contribute to this problem. We must
3 determine how the problem can most effectively be
4 addressed and if rescheduling hydrocodone-
5 containing products is truly the answer and the
6 silver bullet that I talked about before.
7 I think it's an interesting point in fact to
8 know that 100 years of local and federal law and
9 regulations have placed increasing restriction on
10 drug availability and have had limited effects on
11 their abuse and diversion, as we can see by the
12 abuse of this product continuing to grow and
13 increase.
14 Postmarketing surveillance data shows that
15 drugs in Schedule II often have higher rates of
16 abuse, misuse, and diversion than Schedule III
17 hydrocodone products. So I think the numbers that
18 we showed throughout the morning and in this
19 presentation speak to that and speak for
20 themselves.
21 Again, I'll repeat that drug abuse is a
22 complex problem that will require integrated supply

1 and demand side approaches. And finally, in
2 another repeat from the generic industry would be
3 that the partnership among federal and state
4 agencies and regulators, industry, healthcare
5 providers and patients are required to develop an
6 approach that will reduce abuse, misuse, and
7 diversion of hydrocodone-containing products
8 without increasing the burden on the healthcare
9 system and most importantly, the patients who need
10 these products.
11 Thank you.
12 **Committee Questions to Presenter**
13 DR. J. WOODS: Thank you, Mr. Gaugh.
14 I'd like to now proceed with clarifying
15 questions for the Generic Pharmaceutical
16 Association presentation. And I would like to
17 recognize Dr. Lorenz first.
18 DR. LORENZ: Thank you. I think I'm
19 wrestling a little bit with both sides of this
20 question, in particular, what the mechanisms are by
21 which policy would be effective. And I might
22 actually ask you to do something that we queried

1 the DEA about in the last session.
2 You mentioned supply and demand many times
3 together, but treating patients after -- for abuse
4 seems like a weak intervention as a demand side
5 intervention, treating people who have already
6 undertaken abuse as a course of action.
7 I'm wondering if you can help us understand
8 how effective that would be, and if you can
9 suggest, since you yourself raised the issue of
10 integrated supply and demand approaches, what the
11 alternatives would be.
12 MR. GAUGH: Well, if I understand your
13 question correctly, so supply and demand is one
14 piece of it, but to your point, once abuse has
15 occurred, abuse has occurred. So now you're
16 looking at a treatment strategy, and that's not the
17 best for the healthcare system, the patient or the
18 families.
19 DR. LORENZ: Well, not exactly. I guess in
20 terms of reducing the problem of abuse and maybe
21 the consequences of abuse, you suggested
22 interrupting the cycle through treating abusers

1 might change that dynamic. But can you comment on
2 how effective that would be, what you would propose
3 actually in terms of the actionability of that
4 approach and if, in fact, there are other ways that
5 the pharmaceutical association would be willing to
6 act with partners, as you mentioned, to reduce
7 demand side problems with substance abuse?
8 MR. GAUGH: So I think the answer that we
9 have to that is education, and we absolutely would
10 be in support of assisting and providing support
11 for continuing and additional education of the
12 healthcare professionals, number one, and the
13 patients, number two, that we think that would be a
14 key point to it that's not really been addressed as
15 far as what the legislature or the different
16 agencies are trying to accomplish.
17 DR. J. WOODS: The chair recognizes Rose
18 May.
19 MS. MAY: I'm a nurse practitioner that
20 works at the National Institutes of Health, but
21 I've only practiced throughout this area. And you
22 happened to mention about mid-level providers not

1 having access -- or not having the ability to
2 prescribe Schedule II drugs in many states. Now,
3 I've never had that problem. I have a DEA license,
4 and I'm able to prescribe.
5 Can you tell me how many states have the
6 restrictions on nurse practitioners?
7 MR. GAUGH: I don't know the exact number,
8 but I know --
9 MS. MAY: Because I don't think there's that
10 many.
11 MR. GAUGH: I'm sorry?
12 MS. MAY: I don't think there's that many.
13 MR. GAUGH: And there may not be. I don't
14 have that exact number with me.
15 MS. MAY: So when you talk about the person
16 not having access to care, I don't think that's
17 such a big problem. A person has to, of course,
18 apply for it, and some NPs don't apply because they
19 don't want to deal with scheduled drugs.
20 MR. GAUGH: Okay. Thank you.
21 DR. J. WOODS: Other questions?
22 Thank you.

1 MR. GAUGH: Thank you very much.

2 DR. J. WOODS: We'll now proceed to the

3 speaker and guest speaker presentations. Our first

4 speaker is Dr. Michna.

5 **Speaker Presentation - Edward Michna**

6 DR. MICHNA: Well, we're getting to that

7 point in the program where speakers start getting

8 repetitive, and a lot of the questions that the FDA

9 asked me to address have been addressed at least

10 two or three times already. So I might be able to

11 get us back on schedule here or ahead of schedule

12 very quickly.

13 Just a little bit about my background. I'm

14 an academic pain management physician at Brigham &

15 Women's in Boston. I've been practicing academic

16 pain medicine for about 20 years. I started life

17 as a pharmacist. I veered off into the evil world

18 of the law doing medical malpractice litigation for

19 a while until I found religion, and then I thought

20 I'd have to do something more noble with my life,

21 at least that's what I thought at the time.

22 The FDA asked me to give the pain

1 physicians' view on the impact of scheduling
2 changes. And when I was asked to do this talk, I'm
3 thinking, well, the pain physician's probably not
4 the one to ask, right, because we already had the
5 statistics. For me, I don't care if Vicodin is
6 Class II, Class III, Class I. It doesn't matter
7 because my approach to chronic pain management is
8 different than what would be in the community
9 primary care. And I do chronic pain management.
10 As you've already seen in the data, this is
11 mostly an acute pain medicine. I don't write that
12 much Vicodin, to tell you the truth, and that
13 mirrors that data that FDA presented. And the
14 reason for that is in the chronic setting, I'm
15 titrating to effect, and there's thought in our
16 community that patients on chronic opioids should
17 probably be on a long-acting along with it.
18 So the fact that there is not a long-acting
19 hydrocodone on the market really limits its
20 utility, both in chronic pain and in palliative
21 care and cancer therapy. And because of the
22 combination, obviously, there is dose limits. So

1 that's why the utility in my population for Vicodin
2 is much lower than what you would see in the
3 community and certainly in acute situations.
4 That being said, 30 years ago when I was a
5 pharmacist, we were all asking ourselves, why the
6 heck is Vicodin Class III? I mean, even at that
7 time, we had an appreciation that this drug was
8 misused, and we really didn't appreciate much of a
9 difference between it and Percocet in terms of the
10 abuse rates.
11 So I can't tell you how many pharmacy
12 students, residents, medical students have asked me
13 that same question over the years. And I've always
14 responded, well, it is a historical error. They
15 thought it was safer, but it isn't. And that's the
16 way I've approached it.
17 Certainly, when I was a young pharmacist and
18 thinking in a black-and-white world, I would have
19 said, of course, let's just reschedule the drug.
20 And I guess if you work with the DEA, you also have
21 that approach to things. But I think the world is
22 a little bit more sophisticated than that and

1 problematic. And certainly in a clinical setting
2 when you're taking care of patients, particularly
3 after doing this for 20 years, I know the practice
4 of medicine is more involved than just listing
5 eight points and seeing if a particular drug meets
6 those criteria.
7 Pain patients are complex. The practice of
8 medicine is complex. It's influenced by many
9 factors. And certainly as a lawyer, I know there's
10 a lot of things in the law that make absolutely no
11 sense, but they continue to go on and on.
12 Just to reiterate, some things have been
13 said many times and are very obvious. I mean,
14 classification of opioids doesn't stop the misuse.
15 OxyContin is Class II, and it's now -- oxycodone is
16 our most abused drug product. So it's naive to
17 think by reclassifying a drug product, that we're
18 really going to make an impact on it. And it takes
19 a little bit more of a sophisticated look at
20 things.
21 So I was asked to answer these following
22 questions, but, again, a lot of this has been

1 answered, and I'm not going to bore you with it.
2 As we said, most of this drug is used in acute pain
3 settings and very short scripts. I mean, if you
4 look at the prescription data also, I mean, most
5 opioids are written for less than two months. And
6 we already saw the data that was presented both by
7 FDA and other people. And as I said, Vicodin,
8 although used in the cancer population, is
9 certainly not one of the major drugs that we use to
10 treat cancer pain.
11 Who prescribes it? We've already seen, less
12 doctors like me and pain physicians and less
13 oncologists, but more physicians and practitioners
14 that deal with acute situations and acute pain,
15 dentists and post-surgical.
16 Where is it prescribed? Obviously,
17 everywhere. It's the number one prescribed drug,
18 but those of us who were trained on the East Coast,
19 we're more oxycodone oriented. So most of our
20 surgeons from the northeast write for oxycodone for
21 post-op, and in the West and the South, they use
22 more Vicodin. And those are just regional

1 variations that have occurred because you do what
2 you were trained to do, and physicians continue to
3 practice the way they've learned 20 years ago.
4 So why is Vicodin used? Well, certainly I
5 guess in a certain segment of practitioners,
6 there's a false sense that it's safer because of
7 that Class III designation; certainly, the ease of
8 refills and the lack of the restrictions on the
9 Class II opioids. Now, it was talked about earlier
10 about -- I think it's really important on this,
11 too, and some of the secondary unintended
12 consequences that can occur.
13 Doctors are getting the message, don't give
14 a lot of drugs out. But doctors are also
15 overworked and overburdened, and they don't want to
16 be getting phone calls on the weekend that their
17 patient ran out of drug. So if they can't call in
18 a script and it's hard for them to get that script,
19 because of our lack of e-prescribing, to that
20 patient, what is the natural human tendency going
21 to be? Instead of writing for seven days, maybe to
22 be sure, I'm going to write for 14 so we don't have

1 a problem and I don't have to deal with a phone
2 call while I'm watching the Super Bowl.
3 I think it's really important to
4 think -- sometimes we do things and the secondary
5 consequences end up being much more problematic.
6 Certainly, hydrocodone is very tolerated.
7 That's why doctors use it. Although they do have
8 side effects versus some of the other opioids,
9 certainly, more patients tolerate it and don't wipe
10 out on the drug.
11 There's a lot of bad science out there, if
12 you can call this science. This was actually -- I
13 don't know how many of you people saw this. This
14 is a letter in the New England Journal by I believe
15 a psychiatrist, and not based on any scientific
16 data, I think she talked to a couple of her
17 friends. And she wrote a letter saying that
18 doctors are giving narcotics to known abusers
19 because they're afraid of their ratings on the
20 Internet. There was no survey done. There was no
21 statistics, but it was her opinion because she
22 talked to one or two of her friends. And that was

1 published in the New England Journal.
2 So you can see there's a lot of
3 misinformation out there. And certainly, I don't
4 know any of my friends -- I mean, I have the worst
5 ratings on Boston, okay, being a pain physician, I
6 can tell you right now. Nobody says anything good
7 about me. They say that I was the guy that stopped
8 them from getting the drugs that they wanted. So I
9 have horrible ratings, and that doesn't affect the
10 way I practice pain medicine.
11 I was asked to come up with some
12 alternatives. Well, there really is no alternative
13 to Vicodin since, basically, it's a strong opioid.
14 It's a full opioid. Tylenol and codeine, most of
15 the patients vomit on it. I would never take it,
16 but I guess that's an option, although it has a
17 ceiling effect. As we all know, codeine, there's
18 this point where you give more, and you don't get
19 any greater effect from it.
20 Tramadol, certainly not as effective as a
21 full opioid, fraught with a lot of drug-drug
22 interactions if you're on antidepressants, lowers

1 your seizure threshold. Probably not a great drug,
2 particularly in the pain population where 80 to
3 90 percent of our patients are on antidepressants.
4 I guess you could try nonsteroidals, but
5 certainly by the time they reach my population,
6 people have gone through that. And of course, the
7 risk of GI bleed and other complications are not
8 innocuous. And so then you're left with the other
9 Class II opioids.
10 So not being a primary care and not having
11 one up here to express, I will express what I see
12 in the primary care community in terms of opioids.
13 I mean, there's a lot of fear out there, founded or
14 unfounded. At least in the Boston area, the number
15 of patients that are being discharged from primary
16 care practices, because suddenly the practice is no
17 longer running controlled substances, is increasing
18 on a daily basis.
19 Usually of the 40 patients I see a day, I
20 would say at least five of them are patients that
21 were written for prolonged periods in their primary
22 care. And suddenly that doctor left or the

1 practice pattern changed, and now that practice
2 will no longer write for opioids.
3 Certainly, we all know that the primary care
4 writes for most of the pain medicines in this
5 country. And even if a certain fraction of that
6 population stops prescribing, that is not going to
7 be able to be picked up by specialists or any other
8 physicians at that point.
9 They're overworked. They're overburdened.
10 They're paid less and less each year, and they're
11 not getting paid for it. So you have pain patients
12 that require a lot of care and visits that they get
13 very little for. So what is the human tendency at
14 that point? I'm not going to see these patients,
15 or I'm not going to offer that as a therapeutic
16 option.
17 They're confused. Also, they're unaware.
18 Their education levels are all over the place.
19 Some are educated as any academic physician in this
20 area, and others are totally ignorant of some of
21 even the basic things.
22 So if you reschedule hydrocodone, what are

1 some of the other healthcare delivery and access to
2 care issues? Well, certainly it's probably going
3 to result in more frequent visits. Follow-ups, as
4 physicians know, are not paid that well; again, a
5 negative psychological effect on taking care of
6 these patients. And from a physician's standpoint,
7 for every follow-up that they see, it's one less
8 initial or a higher paying reimbursed visit.
9 As I spoke about earlier, there is
10 decreasing willingness in that primary care setting
11 to provide these medications for these various
12 reasons.
13 The whole thing about e-prescribing is
14 really important. If that was an option, then
15 these weekend issues, these Friday night issues
16 could be more easily handled since Vicodin can be
17 called in and a Class II narcotic, they can't. In
18 the middle of the night, there's no way that
19 patients -- or late in the evening, there's no way
20 these patients are going to be able to be
21 physically handed a script.
22 Nursing home issues, we had this

1 happen -- what was it, last year or year or the
2 before -- about the lack of physicians actually
3 having handwritten prescriptions. Again, I don't
4 know what percent of nursing home patients are on
5 Vicodin, but there again is another issue; again,
6 another hurdle that will have to be solved if this
7 rescheduling is going to go on.
8 Also, for Class II scheduled substances,
9 each state has extra regulations that might require
10 more time and effort. Again, a chilling effect on
11 physicians' willingness to provide this as a
12 therapeutic option.
13 In each state, there's various regulations.
14 In Massachusetts, we have a regulation for Class II
15 scheduled substances, that the patient has to be
16 seen more frequently, has to be reevaluated in
17 person every four months at least, and you need to
18 speak directly with the primary care or any other
19 possible treating physician. Now, I can tell you,
20 you go to most physicians in Massachusetts, and
21 they don't even know about this regulation, which
22 leads you to the point where sometimes regulators

1 don't communicate very well except when they're
2 holding you in violation of regulations. But
3 again, another burden that may or may not be
4 appropriate.
5 I think we have to -- since this is such a
6 complex problem, we have to approach it by many,
7 many aspects. And this has already been said,
8 right? There are no simplistic answers to this.
9 Education is crucially important. It has to start
10 in medical school, and it has to work its way
11 through. And it's going to take years to do this.
12 It's not going to happen overnight. I wish it
13 could, but it's not going to. And physicians later
14 in life, as we -- my age, we don't adapt very well,
15 and we don't change even with education. So this
16 is going to have to work its way through the
17 system.
18 Certainly, we have a whole protocol of what
19 we do, and I'm in the ivory tower, right? I mean,
20 I have everything at my access. I have pain
21 psychologists. I have multiple specialists that I
22 can have patients sent to. We have 24-hour

1 pharmacies. I have basically all that I would
2 need, so it's easy for me to pontificate on how to
3 approach the opioid abuse problem and what you need
4 to do to control it. But certainly, that can't be
5 applied universally across the country because a
6 place like this is certainly very different than
7 Boston. There's probably not a 24-hour pharmacy.
8 There's probably patients that have to drive
9 hundreds of miles to get to a practice.
10 So you can see where a drug that's Class III
11 might have greater utility because of these
12 physical limitations in access. And the fact that
13 it makes sense to do something, we also have to
14 think about who's taking advantage of those -- the
15 advantages of that scheduling and how do we
16 mitigate the impact on those people or those
17 patients if we go forward with the scheduling
18 change?
19 So it's all about balance. I think balance
20 has been used by several of the other speakers. I
21 think if we -- if you or the regulators go forward
22 with a change in this, I think we need to address

1 those issues that I brought out. Reimbursement for
2 taking care of these patients has to be improved.
3 And certainly, education is a major component in
4 this, and it's going to take years. And research.
5 If we don't put money in the research, we're never
6 going to know anything. And you can see how much
7 lacking data we have on all this. It's based on
8 the fact that we haven't spent the research dollars
9 to really look at this problem in depth.
10 So I want to leave you with a quote from
11 Osler, "It's more important to know what type of
12 person has a disease than to know the disease a
13 person has." And in all of medicine, and
14 particularly in the pain world, it's about
15 individualized care. And we have to keep that in
16 mind. As the individual, there's so much
17 variability in the psychological and social issues
18 in pain that we have to have the ability for
19 physicians to be flexible in their approach. And I
20 thank you.
21 DR. J. WOODS: Thank you, Dr. Michna.
22 Our next speaker is Eric Lavonas.

1 **Speaker Presentation - Eric Lavonas**

2 DR. LAVONAS: Good afternoon and thanks.

3 I'm Dr. Eric Lavonas. I'm an emergency room

4 physician and a medical toxicologist and a drug

5 safety researcher from the Rocky Mountain Poison

6 and Drug Center from Denver Health and Hospital

7 Authority. And I would point out that it's

8 62 degrees and sunny in Denver, and we don't know

9 what you're doing here.

10 (Laughter.)

11 DR. LAVONAS: So FDA asked me to talk about

12 prescription drug monitoring programs, in

13 particular, to critically evaluate their role as a

14 tool in helping with the problem of prescription

15 opioid abuse. Dr. Toliver has already covered by

16 disclosures, so I think I'll move on.

17 What we're going to talk about in the next

18 19 and a half minutes or so is the

19 structure -- talk about what prescription drug

20 monitoring programs are to kind of bring everybody

21 to the same page. I'm going to go very quickly

22 over some of the key articles in the literature,

1 and then provide you with some new data that we
2 developed specifically for this hearing about the
3 effect that -- or about what we observed in states
4 that do and don't have prescription monitoring
5 programs, and then the knowledge gaps and future
6 directions.
7 So prescription drug monitoring programs are
8 a White House designated priority strategy as one
9 of the strategies to help respond to the problem of
10 prescription drug abuse. And so there's about
11 315 million Americans, and we are unified around
12 one thought. That one thought is I'm the most
13 important person of the 315 million Americans, and
14 it all revolves around me. That was supposed to be
15 funny. I'm sorry.
16 (Laughter.)
17 DR. LAVONAS: And as one of the 1.1 million
18 physicians who absolutely feels that way, from my
19 perspective as an emergency physician, prescription
20 monitoring programs are used to help me identify
21 problem pain behaviors, and, in particular, to help
22 me either rule in or rule out truthfulness.

1 Studies by Barons, for example, have shown what my
2 clinical experience shows, that about half the time
3 when an emergency physician consults a prescription
4 drug monitoring program, and it results in
5 prescribing less opioid medication for the patient.
6 And about half the time, we prescribe more because
7 we've been able to verify that the patient is
8 telling us the truth and that frees us to be more
9 responsive to the patient's needs.
10 So these programs are set up state-based
11 with partial federal funding. They're designed to
12 monitor the behavior of patients and/or providers
13 by automatically capturing prescription fill
14 information, collating it at the patient provider
15 level and then allowing it to be queried.
16 That's kind of where the similarities end.
17 Most of these programs are run by state health
18 departments. Some are run under law enforcement, a
19 few under boards of pharmacy. They vary widely in
20 their ease of use. Some will send out unsolicited
21 reports. Others require a practitioner to query.
22 And integration between states is a promise that is

1 finally being fulfilled but isn't quite there yet
2 for most of the country.
3 So 44 states have operational PMPs. Five
4 more are getting close. I'm not sure what's going
5 on with Missouri. And there have been a few
6 evaluations published out there of the
7 effectiveness.
8 So two very similar studies, one by Simeon
9 and one by Reisman, that basically took the same
10 approach of taking about six years' worth of data
11 across the country, classifying states as having or
12 not having an active prescription monitoring
13 program, and then looking at two outcomes. One was
14 the total quantity of opioid medications supplied
15 to the state divided by population, and the other
16 is treatment admissions using SAMHSA's TEDS data
17 sets, so treatment admissions for prescription
18 opioid abuse.
19 The two studies, it's always nice when two
20 studies with similar goals and methods come to the
21 same conclusion, and they did; that in the states
22 that had functioning prescription drug monitoring

1 programs, there was less increase in shipments for
2 Schedule II opioids. And the studies really looked
3 mostly at Schedule IIs. And also, less increase in
4 treatment admissions for prescription opioid abuse
5 compared to the states that did not have PMPs.
6 So the most talked about study in this area
7 comes from some CDC researcher, so I'm going to
8 spend a little more time about it in part because
9 the conclusion is different than the data I'm going
10 to show you. So Len Paulozzi, Ed Kilbourne and
11 colleagues in CDC did an ecological study with very
12 different outcomes than the others.
13 So again, they took 50 states times six
14 years, and each state year pairing was classified
15 as either saying PMP active yes or no. And then
16 also, if there were unsolicited reports sent, then
17 that became a proactive prescription monitoring
18 program, sort of look for dose effect. And they
19 again looked at drug supply in milligrams of
20 morphine equivalent per capita and also deaths from
21 unintentional overdose in the CDC's WONDER
22 database.

1 Very important, because this is the big
2 methodologic difference between the Paulozzi study
3 and what I'm going to show you in a bit, basically,
4 what they did was created two grand categories, PMP
5 active for that year in that state or not, and then
6 averaged the rates instead of looking at trends
7 over time.
8 Before we get into the results, though, the
9 big picture here is enormous. Over this six-year
10 period -- and this is older data now. But over the
11 six-year period, the amount of opioids prescribed
12 and dispensed to residents in the United States
13 tripled up to 525 milligrams of morphine equivalent
14 per capita in the United States. That's a lot of
15 medicine. Not surprisingly, the same time period,
16 opioid analgesic overdose death rates tripled,
17 also.
18 But Paulozzi and colleagues using their
19 methods didn't find any apparent relationship
20 between the prescription monitoring programs and
21 their outcomes. So here looking at sales, the top
22 pair of parallel lines are the Schedule IIs; the

1 bottom pair of parallel lines are hydrocodone. You
2 can see over this period a lot greater increase in
3 the Schedule IIs but no apparent effect of the
4 PMPs. And the same with death rates. Here, the
5 bottom pair of lines are the prescription opioid
6 overdose deaths. And again, the lines are
7 parallel, so no apparent relationship between the
8 presence of a PMP and overdose mortality.
9 So why not? I think some of it is
10 methodologic and some of it have to do with the
11 PMPs themselves. For methodologic, getting back to
12 this decision to look at average rates, given that
13 places that have a problem tend to implement a
14 solution, if a state has high rates for several
15 years, implements a prescription monitoring
16 program, unless the rates go very, very quickly to
17 very low, some of those year quarters are going to
18 be really dealing with the effects of a long-term
19 established problem, which is going to -- it's a
20 decision that the researchers made, which was
21 conservative and made a lot of methodologic sense,
22 but in this case may have caused beta error, may

1 have made it possible that they missed a true
2 treatment effect.
3 Then we'll talk about some of the things
4 with PMP status of the states. Nobody has really
5 ever been able to grapple with the idea of how long
6 after a prescription monitoring program is turned
7 on can you expect it to really have benefit.
8 But other big issues happened. One is the
9 programs, especially during this time period, were
10 very, very underutilized. I'll show you some data
11 in the next slide. Some states during this period
12 were not even allowing prescribers to access the
13 data. So if you'd like your prescribers to
14 prescribe better, you kind of have to show them the
15 data. And by that, I mean individual patient
16 reports.
17 I have to always remind myself, since I live
18 in a large square state where all the population is
19 in the middle, that the problems and solutions in
20 my state are different than, say, in the northeast
21 where it's much easier for these problems to cross
22 state borders.

1 So what do I mean by low utilization? So
2 Tracey Green and colleagues really drilled down on
3 this. Of all of the states with prescription
4 monitoring programs in the Paulozzi study, the
5 busiest program was Kentucky's, which had three
6 inquiries per thousand population per year. Hard
7 to combat an epidemic with that level of activity.
8 And five of the states were classified in this
9 study as having prescription monitoring programs,
10 but they were law-enforcement-only programs that
11 were not accessible to the provider.
12 So one more. This is an example -- this is
13 not a prescription monitoring program study, but
14 it's a great example of what could work. This is
15 an actual experiment in British Columbia that
16 actually happened in the '90s, but Dormuth and
17 colleagues wrote it up last year, in which the
18 provincial government of British Columbia
19 instituted a new pharmacy benefit software. And
20 when that software went live, the pharmacist
21 adjudicating a claim, any drug, got to see a list
22 of all of the other drugs this patient had filled.

1 Very, very rapidly, the number of
2 inappropriate opioid prescriptions using a strict
3 definition dropped by about a third simply by
4 providing information that was in the work
5 flow -- in this case of a pharmacist -- but in the
6 work flow of one of the healthcare professionals
7 involved in that patient's care. So I think this
8 shows us what ease of data can do.
9 So for this presentation, we did a targeted
10 analysis. We're using here quarterly data from the
11 RADARS system. It's our prescription drug
12 diversion of use, misuse surveillance system.
13 Here, we compared -- we broke our data into states
14 and quarters and classified each state as having or
15 not having an operational PMP in that year or
16 quarter. And the big difference between this and
17 the Paulozzi methods are that we looked at rates
18 quarter over quarter, so we compared Q2 to Q1. We
19 compared Q4 to Q3 and said what was the change.
20 And then I annualized this just because it's a lot
21 easier to talk about annual changes.
22 Two main data streams, one is the RADARS

1 systems poison center program. Fifty out of the 57
2 poison centers in the United States contribute case
3 level data to our program. So the coding is
4 initially performed by pharmacists or nurses
5 working in the poison centers. As soon as they
6 come in our door, they are subjected to quality
7 control to make certain that all of our coded data
8 fields match the source document.
9 In this case, one case in this program or
10 one event is one person exposed to a prescription
11 opioid that then resulted in a call to a poison
12 center. And for this analysis, I looked at only at
13 the intentional abuse cases, so these were only
14 people where the reason for exposure was an attempt
15 to get high.
16 I'm not saying that self-harm attempts or
17 accidental misuse, misadventures, or any of those
18 things aren't important, but here I'm looking
19 specifically and only at exposures for the purpose
20 of abuse.
21 We also took data from our two treatment
22 center programs. So the opioid treatment program,

1 patients are entering the federal treatment program
2 system, and the skip patients are entering private
3 drug treatment programs. Between the two, we've
4 got about 200 programs. Patients entering these
5 programs are offered the chance to complete a
6 survey about their drug use.
7 We ask them to list every specific drug that
8 they used to get high in the previous 30 days.
9 They also designate a primary opioid, but in this
10 case, I looked at all opioids. So a patient there
11 could be in both categories if the patient endorsed
12 hydrocodone and oxycodone use in that month, for
13 example.
14 So we looked at hydrocodone and then the
15 Schedule IIs as a group, population rates and also
16 a supply-adjusted rate. When we do supply-adjusted
17 rates, we look on the denominator of patients
18 filling prescriptions, or URDD, same thing, because
19 we feel that patients are the ones who derive
20 benefit from appropriate therapy, and patients are
21 the ones who make a decision to divert or misuse a
22 drug. And again, these are exponential increases

1 over time.
2 So without trying to stray with the laser
3 pointer here, let me just kind of walk you through
4 this slide. So these are intentional abuse
5 exposures in the poison center system. If you look
6 over hydrocodone at the red bar, this is the annual
7 change in rate of intentional abuse -- calls to
8 poison centers for intentional abuse of hydrocodone
9 in states without a prescription monitoring
10 program. And you can see that rate has been
11 increasing at about 7 percent per year in those
12 states.
13 In the states that had functioning
14 prescription monitoring programs, the decrease was
15 about 1.4 percent per year, so a very significant
16 apparent difference between the two sets of states
17 and a very similar pattern for Schedule II opioids.
18 Now, one question that we all want to know
19 is, is this just a nonspecific chilling effect? If
20 you put a PMP in place, do you see just fewer
21 prescriptions overall? And because we don't want
22 to decrease access for patients to medicines that

1 are benefitting them, we want to improve the
2 targeting of this. So you'll notice that these
3 bars are across the board less than or smaller
4 than, shorter than the rates or less than the slide
5 before.
6 What this tells us is that the increase in
7 supply -- that the number of patients filling
8 prescriptions increased faster than the number of
9 calls to poison centers for intentional abuse. So
10 that's a good thing. However, there was not a
11 fundamental change in the relationships between the
12 PMP and non-PMP states. So we're not as certain
13 that this benefit was related to the PMPs.
14 Similar source of pattern in the treatment
15 programs, the orders of magnitude more difference.
16 The treatment program admissions for hydrocodone
17 abuse increased at a rate of 24 percent per year in
18 states that did not have prescription monitoring
19 programs and just a little less than 12 percent per
20 year in the states with PMPs, again, a significant
21 difference.
22 Not as much effect when you do a supply-

1 adjusted analysis, but again, the increase in
2 prescriptions does seem to be outpacing the
3 increase in treatment admissions.
4 So you don't know what you know till you
5 know what you don't know. These are observational
6 studies. Therefore, we can't say that A causes B.
7 We can only say A is associated with B. I have to
8 acknowledge the limit that not all prescription
9 monitoring programs covered hydrocodone for all
10 these years, so some of those may be misclassified.
11 Like everybody else, we couldn't really deal
12 with the run-in period nor with supply that either
13 comes across state lines or supply that's not
14 reported to prescription monitoring programs, such
15 as most of the federal health agencies such as the
16 VA, though that seems to be changing.
17 So in conclusion, basically, prescription
18 monitoring programs seem to show promise as a tool
19 to reduce prescription opioid abuse. Certainly,
20 opioid abuse rates or ratios rise less quickly in
21 the states that have a PMP compared to those that
22 don't. There doesn't seem to be a fundamental

1 difference between hydrocodone and the
2 Schedule IIs, but at least some of this is not just
3 a chilling effect on supply.
4 Again, we don't know whether what we see is
5 causal. There are multiple things going on
6 simultaneously in a state. We don't really know
7 what features make a PMP most effective. We have
8 surprisingly little data on how much the
9 prescription monitoring programs are actually
10 utilized by practitioners and also wonder whether
11 we're assessing the right harms. I mean,
12 certainly, if you're looking at overall supply,
13 that cuts two ways because there's patients
14 benefitted and patients harmed.
15 Deaths, clearly, we all agree are harm, but
16 if hydrocodone abuse goes down and oxycodone abuse
17 goes up and heroin abuse goes up, then you've got a
18 very complex calculation. And I don't think our
19 data really can answer that, but clearly, we do see
20 shifts to other opioids when one becomes harder to
21 abuse, and that's going to have to be wrestled
22 with.

1 What might make prescription monitoring
2 programs more effective? Well, one would be
3 including all of the sources, including VA and
4 Indian Health Service and treatment programs and
5 all of that. Another would be increased
6 utilization by providers. I'm very good at using
7 the Colorado PMP. It takes me about three minutes
8 from when I sit down at a terminal to when I'm
9 looking at a patient report, and then I can read it
10 pretty quickly.
11 Three minutes is a very long time if you're
12 a primary care physician seeing four or five
13 patients an hour. Giving yourself 12 to 15 minutes
14 of cycle time per patient, it just doesn't work.
15 In my state, delegated access is illegal. I cannot
16 ask someone to pull a report for me.
17 Automatic integration into the electronic
18 medical record and summary scores and other things
19 that make it easy to screen and only spend -- for
20 the practitioner to spend time where the time needs
21 to be spent will definitely make these more
22 effective as they come over time.

1 So the acknowledgement slide is always a
2 good sign your speaker is about ready to stop
3 talking. I'd like to acknowledge the people that
4 actually did the work, including our biostatistics
5 team, the principal investigators for our various
6 RADARS system poisons, and also, a big thank you to
7 the National Association for Model State Drug Laws,
8 who's helped us and basically everybody else who's
9 researched this topic.
10 So in summary, the preponderance of evidence
11 does support that there is a likely clinically
12 meaningful impact to prescription monitoring
13 programs, that they reduce the increase or mitigate
14 the problem of prescription opioid abuse.
15 Hydrocodone and Schedule II opioids seem to be
16 similarly effective, but PMPs alone are not going
17 to be the solution, only a part of the solution.
18 I guess we'll take questions after the next
19 speaker. Thank you.
20 DR. J. WOODS: Thank you, Dr. Lavonas.
21 Our next speaker is Dr. Zacharoff on
22 education and its role in this complex system.

1 **Speaker - Kevin Zacharoff**

2 DR. ZACHAROFF: Thank you, Dr. Woods. And
3 it is an honor and a pleasure to be here speaking
4 to you and the panel today on this subject which is
5 very near and dear to my heart.
6 A little bit of background about me. Like
7 Dr. Michna, I have over 20 years of clinical
8 experience in anesthesiology and pain medicine.
9 The last eight years of my life have been entirely
10 devoted to education in some way, shape, or form.
11 I am the vice president of medical affairs at
12 Inflexxion, but I also am faculty and clinical
13 instructor at Stony Brook School of Medicine in New
14 York.
15 I think it's important to say that next
16 Tuesday I will -- I teach medical ethics there.
17 And I will be covering the topic of compassion in
18 the art of healing. And that is not something that
19 I was taught to do in medical school. It is not a
20 subject that was broached when I was a medical
21 student, and I would venture to say that a lot of
22 people who are my contemporaries didn't learn it,

1 either.

2 But there is a feeling that these kinds of

3 things are important to teach to students today so

4 they can make a difference tomorrow. And from an

5 ethical perspective, we spend six months teaching

6 them processes that could be applied to ethical

7 decision making in a repeated, reproducible way.

8 And I would make the argument in this talk,

9 hopefully to you, that we have an opportunity to do

10 the same thing with respect to pain management, and

11 it is not happening yet in our environment.

12 Now, I did mention to a couple of

13 acquaintances that I was coming here to give this

14 talk today on behalf of FDA, and one of them was a

15 primary care doctor in rural upstate New York. And

16 she said to me that my fear about the rescheduling

17 of hydrocodone is the increase that would result in

18 the cost of care to her patients and the healthcare

19 system.

20 I also happened to mention it to an

21 acquaintance who is very much an expert in the pain

22 arena who said to me, "I find it very interesting

1 that education is even going to be discussed at
2 this meeting. What does education have to do with
3 this subject?"
4 So I don't know that I'm going to convince
5 you that education is the single solution. It
6 isn't. It's one of the solutions, but hopefully,
7 we'll at least explore the fact that in terms of
8 education and pain management today, there are some
9 dramatic deficits.
10 The first question I think worth posing is,
11 where does pain education live today? I think in a
12 number of our minds, it lives in a variety of
13 different places. In some cases, it's in national
14 meetings. In other places, it's online continuing
15 medical education programs. But does it really
16 have a single home? Is it like this foundational
17 course on medical ethics that I teach? And if it
18 doesn't live somewhere, then it's possible that
19 it's fragmented and it may indeed have no real
20 home, which, in my mind, is one of the real
21 problems.
22 Now, if we take a look at the landscape, a

1 number of speakers have already mentioned today
2 that when we look at pain management, we could
3 break healthcare providers up into two groups: the
4 experts who have all the training and have all the
5 knowledge and get together and discuss issues and
6 lack of research and so on and so forth, and then
7 the non-experts, which is really the lion's share
8 of the group of healthcare providers that are being
9 faced with these patients who have chronic pain.
10 One of the panelists mentioned earlier today
11 that one of the most frequent reasons for a visit
12 to a healthcare providers is a pain-related
13 complaint. And it goes without saying that most
14 times, these are primary care clinicians that are
15 seeing these patients. And similar to some of the
16 earlier statistics presented today, the prescribing
17 is being done by primary care practitioners by and
18 large.
19 One thing I don't often hear mentioned,
20 though, is the state of pain management from an
21 institutional versus an outpatient perspective. A
22 colleague of mine, Jeff Applebaum, published an

1 article back in 2003 in Anesthesia and Analgesia on
2 a survey that was done of inpatients who were post-
3 surgical and their ratings of pain management post-
4 operatively within their hospital stay. And three-
5 quarters of the patients surveyed had moderate to
6 severe pain despite all of the tools that were
7 available to manage this pain in the hospital
8 setting.
9 Well, not a lot has changed nine years
10 later. I am working with a number of institutions
11 who tell me that their HCAP ratings and their pain
12 management scores in terms of the service they're
13 providing to their patients is abominable. And
14 what makes me a little bit nervous is that when I
15 bring up a sentinel alert that was sent from the
16 Joint Commission to all hospitals in the country
17 back in August 2012 on safe use of opioids, I have
18 yet to speak to someone who works in a hospital
19 that's even aware of the fact that this was sent
20 out.
21 So the education has a variety of different
22 homes. Well, where is it? Well, many people feel

1 that it's really not there at all. And certainly,
2 as Dr. Michna mentioned, in the medical school
3 setting, it's all but pretty much absent. In my
4 medical school, we have one day of four years'
5 medical education devoted to pain management. One
6 hour of that one day is devoted to opioids, and
7 it's mainly pharmacology, and zero hours are
8 devoted to aberrant drug-related behaviors,
9 addiction, et cetera. And a number of studies have
10 borne this out. When they looked at the percentage
11 of medical schools currently reporting having
12 courses on pain management, only 4 percent of U.S.
13 medical schools reported that they have a
14 curriculum in place.
15 When medical students were polled,
16 59 percent said they rated their medical school
17 education on pain management as fair or poor. And
18 this translates into lack of confidence in
19 clinicians when they graduate from their training,
20 and they cite many reasons: lack of preparation, a
21 number of barriers that they were faced with that
22 they never knew were coming, learning about federal

1 and state regulatory restrictions once they're
2 already swimming in the pool of pain management
3 instead of being taught about them before they got
4 to that point.
5 When attending physicians were polled and
6 they were asked to rate their medical education,
7 over 80 percent in one study found that their
8 medical school education was inadequate, and only
9 one-third of those primary care physicians actually
10 screened patients who were being considered for
11 chronic opioid therapy for substance abuse.
12 When I look at experts and primary care
13 providers, I definitely see that they have some
14 aspects in common. We've heard earlier today,
15 obviously, economics is an issue. Everyone has
16 time constraints if they're practicing in the
17 healthcare environment today. Pretty much everyone
18 also has a high patient volume and tremendous
19 economic challenges.
20 But when we did some research and we spoke
21 to experts and we spoke to primary care physicians,
22 we got some different answers with respect to pain

1 management. The experts told us, we do not need
2 education. Obviously, we know what we're doing,
3 but we need tools and we need things that can help
4 us be more efficient. When we asked the same
5 questions to primary care providers, they said, we
6 need guidance on telling us what to do. We need
7 this to somehow be made more clinically relevant
8 for us so we could figure out how this fits into
9 our practice.
10 A number of people think if we take this a
11 step further and we look at the progress in our
12 educational system with respect to addiction and
13 aberrant drug-related behaviors and substance
14 abuse, that we're somewhere in the early 1900s in
15 terms of where we are in terms of progress.
16 So where should the education come from?
17 Well, I can tell you this. Most primary care
18 providers I know don't get the Journal of Pain
19 every month, and they don't get issues of Pain
20 Medicine. And when guidelines come out and when
21 meetings like this take place, they do not know
22 about this. Many of the primary care providers

1 that I have the good fortune to speak to over the
2 course of the year don't even know what REMS is and
3 they never heard of it.
4 It's definitely true that they feel that
5 it's a major challenge for them. They do see
6 things in the media. Sometimes things do trickle
7 out into the publications that they do receive, but
8 it took a year for an article to appear in JAMA
9 about REMS. These things are very slow in coming
10 to the people on the frontline of healthcare.
11 It's also interesting, we did a study and we
12 queried pain experts, and we queried a set of
13 primary care clinicians about what they thought
14 were the 10 most important topics that primary care
15 providers should be educated about with respect to
16 managing chronic pain with opioids. And what we
17 found was that both groups thought management of
18 pain and comorbid conditions was far and away the
19 most important topic to cover, but when we went
20 down the line, there was a large diversity in terms
21 of the answers. And there wasn't a lot of
22 correlation.

1 So developing curricula that's intended for
2 primary care, that's entirely designed by pain
3 experts, may not actually coincide with what the
4 primary care clinicians think they need to learn
5 and where they see their deficits in knowledge are.
6 So a word about guidelines. This is one
7 article that looked at whether or not
8 implementation of guidelines in a primary care
9 setting had any impact on the way that primary care
10 clinicians in a certain institution manage
11 musculoskeletal pain. And it did not. And I would
12 also say that most people I know personally and
13 most people I've spoken to feel that just the
14 development of guidelines don't really make a
15 difference because they're not well disseminated,
16 they don't resonate well with what they non-experts
17 need to do in their daily lives. And in some
18 situations, when they hear they have a low evidence
19 basis, there's not the motivation to incorporate
20 them into their practices.
21 With respect to tools, we found actually the
22 same thing. I presented a paper with the Kaiser

1 Foundation back in 2008 at the American Pain
2 Society meeting. They had made the decision to
3 incorporate our SOAP tool for screening for the
4 likelihood of aberrant drug-related behavior into
5 the Kaiser system. And we took a look about a year
6 later after implementation, and what we found was
7 that just making the tool available to the
8 clinicians didn't actually change the course of
9 practice. And in many situations, it wasn't even
10 utilized at all. What we found was that without
11 the educational foundation showing the clinicians
12 why the tools should be used, it almost fell on
13 deaf ears.
14 So do we feel that education can make a
15 change? Well, I certainly do. And my approach to
16 this is that in order for education to be
17 effective, we need to not only go and teach it to
18 people who are in training so they carry it through
19 their career with them; we need to present people
20 who are in practice now with paradigms that they're
21 familiar with. And I use warfarin as a good
22 example of that.

1 I think when a primary care provider is
2 faced with the decision of prescribing an
3 anticoagulant for somebody, they have a set of
4 things in their mind that they know they need to
5 talk about with the patient. They need to take
6 about risks. They need to talk about benefits.
7 They need to talk about monitoring. They need to
8 talk about follow-up care. They need to talk about
9 other medications the patient might take and so on.
10 I think that if we taught pain management in
11 a similar way with respect to assessment, informed
12 decision making, informed consent, monitoring
13 requirements, and this resonated with the
14 clinicians, they would approach it just like they
15 approach anticoagulant therapy.
16 We need to teach them frameworks that they
17 are familiar with and that work for them. One of
18 the things that I was schooled in recently, I was
19 having a discussion with a primary care provider in
20 New Mexico, and I was using the term "opioid risk."
21 And I was really thinking I was referring to
22 aberrant drug-related behavior. And he stopped me

1 in midsentence and said, "I consider opioid risk to
2 be constipation, nausea, vomiting and respiratory
3 depression. When did the definition of opioid risk
4 change?" And he made me think twice.
5 A lot of clinicians out there, just like
6 when I was trained, consider opioid risk to be the
7 risk of adverse effects. It's actually both.
8 These clinicians just weren't taught about the new
9 definition of opioid risk, but the old definitions
10 haven't disappeared. They're just not front and
11 center.
12 Obviously, patient education is a critical
13 piece of this puzzle, and we need to consider the
14 fact that we make primary the goal of teaching
15 clinicians to teach patients. It's their role to
16 teach patients responsibilities and learn how to
17 get patients engaged and know what to do. A lot of
18 things we've heard discussed today could happen to
19 pain medications when they're taken home and put
20 into a medicine chest or that kitchen drawer that
21 everybody has access to. But I do not know anyone
22 who has ever told a patient, here's what I want you

1 to do with the unused portion of your prescription
2 pain medication. It's almost as if we consider it
3 to be implied that you're going to hold on to it
4 and keep it for future use. We need to teach
5 patients about medication safety, about adverse
6 effect recognition, breakthrough pain, what goal
7 setting is, and what goals patients should expect.
8 So in conclusion, educational emphasis in
9 pain management should also focus on medication
10 safety as evidenced by a number of studies.
11 Currently, there aren't any educational mandates.
12 There are only educational offerings. And it's
13 certainly my feeling that meaningful education can
14 be achieved in a variety of ways, such as the FDA
15 mandated opioid risk mitigation strategies.
16 It's a wonderful step. But it's continuing
17 education. And my argument would be that
18 continuing education is a good supplement to
19 foundational education, but it's not a replacement
20 for foundational education. We need a well-
21 coordinated effort as opposed to fragmentation.
22 Thank you.

1 **Committee Questions to Presenters**

2 DR. J. WOODS: Thank you, Dr. Zacharoff.

3 I think we want to take some questions for

4 the last three presenters, actually, and the first

5 person I'd like to call on is Dr. Simoni-Wastila.

6 DR. SIMONI-WASTILA: Dr. Simoni-Wastila,

7 that's a tough one. Thank you.

8 I have a question for Dr. Lavonas, actually,

9 a couple comments and questions. And I'll wait

10 till they all come up to the front.

11 DR. LAVONAS: Proof you can never get three

12 physicians to do the same thing the same way.

13 DR. SIMONI-WASTILA: That's right. Really

14 appreciated the discussion on prescription drug

15 monitoring programs because they are so widespread,

16 and the comment I have is about PDMPs are not

17 created equal, as you recognized in your talk. But

18 in Paulozzi's work, he did find that three programs

19 did have an impact on mortality. Those were the

20 states of California, Texas and New York. And part

21 of the reason that they did have an impact -- and

22 that's a reduction in mortality -- was because they

1 are structurally different than many other
2 prescription drug monitoring programs, which only
3 rely on electronic mechanisms. These also have
4 some sort of serial prescription overlay or
5 something like that.
6 And I think that's one area to think about
7 when we go further and think about rescheduling
8 because essentially what prescription drug
9 monitoring programs are, in a way, is sort of like
10 a rescheduling of sorts in that we're paying closer
11 scrutiny to some medications.
12 I was wondering in your work, in the review
13 of the programs that you had looked at and the
14 studies that you had looked at, had you -- you've
15 demonstrated that prescription drug monitoring
16 programs do seem to reduce the supply or at least
17 the utilization of the opioids. And I was
18 wondering if you were able to see from those
19 studies, tease out more definitively the
20 differences in actual reductions and sort of abuse
21 and diversion, and then what influence they might
22 have on the reductions of access to these

1 medications for people with medically indicated
2 need for such medications, as well as any medical
3 treatment outcomes. I was wondering what you might
4 have discovered in your review of that.
5 DR. LAVONAS: I would love to have the data
6 to answer all the questions you just asked, and we
7 don't. Unfortunately, what we know about
8 prescription monitoring programs at this point is
9 very much at a crude sort of 10,000 feet level.
10 We know that from one small study in
11 emergency physicians that about half the time,
12 prescribers will prescribe more and about half will
13 prescribe less medication when that data becomes
14 available. We have the Canadian experience, and we
15 have sort of the other studies I just presented.
16 What we found with the -- so when I showed
17 slides that had population rates and then rates
18 based on the number of patients filling
19 prescriptions, what we found is that across the
20 board, the number of patients filling prescriptions
21 is going up faster than the number of either
22 treatment admissions or calls to poison centers

1 related to prescription opioid abuse.
2 So that's a big picture improvement if you
3 believe, as I do, that the number of people who
4 gain benefit from prescription opioids exceeds the
5 number of people who are being harmed by them. I
6 think most people would agree with that. It'd be
7 very hard to find any data that would say that
8 ratio is flipped.
9 Nonetheless, we absolutely can do better.
10 We have an enormous problem, and the nut that we
11 all need to crack here is how to prevent the harms
12 of prescription drug dependence, the misuse, abuse,
13 addiction, death, while still maintaining
14 adequate -- maintaining might be
15 optimistic -- while still providing adequate pain
16 control to patients who legitimately need it. I
17 think PMPs are one tool, but we don't know enough
18 about them to be able to answer those questions.
19 DR. SIMONI-WASTILA: Thank you. Do you have
20 any sense of if hydrocodone was rescheduled from
21 III to II? Because many of the studies that you
22 just cited really focused on the Schedule IIs,

1 other than the work you had done with RADARS. Do
2 you have a sense of what substitution patterns
3 might come up? Because some of those studies that
4 you looked at did look at substitution patterns
5 when drugs were scrutinized under PDMPs. And I was
6 wondering if you had a sense of what might happen
7 when you couple that with a prescription drug
8 monitoring program and what -- when you squeeze the
9 balloon of all analgesic prescribing, what might
10 happen.
11 DR. LAVONAS: You said "squeeze the
12 balloon," yes. So the great thing about when
13 somebody asks what might happen is you can say I
14 don't know, and I don't know. We do have several
15 other examples of where one or another opioid or
16 access strategy became a hardened target, and what
17 we observed in each of these is exactly what you
18 said, squeezing the balloon.
19 So people who are already well along that
20 continuum from dependence to addiction, et cetera,
21 will seek other avenues for opioids. I think
22 that's fairly clear, and whether they shift to

1 oxycodone or shift to heroin, I don't know. Or
2 tramadol. They may go down the analgesic ladder.
3 But I think that's pretty solidly predictable. I
4 think all the previous experiments show something
5 like that.
6 The harder part that I don't know is about
7 initiators. When you have somebody who is not
8 dependent, is not addictive, is not anywhere on
9 that spectrum, yet who gets the first prescription
10 for an opioid analgesic that would have been
11 hydrocodone before and now perhaps isn't. Some of
12 those patients will get oxycodone as their first.
13 Some will get tramadol. Some will get a scattering
14 of other things. And what happens to those
15 patients and whether there will be a net benefit or
16 a net harm is impossible to say. And I've been
17 scratching my head about that for the last nine
18 months, and I still don't have a good answer for
19 you.
20 DR. SIMONI-WASTILA: Thank you.
21 DR. J. WOODS: Dr. Maxwell.
22 DR. MAXWELL: A comment and then a question

1 for you. Dr. Lavonas, I think you might have a
2 really interesting methodology, but I'm a little
3 troubled because, according to this, Texas has an
4 active prescription monitoring program which
5 consists of sending in the questionnaire by snail
6 mail and maybe you get a response a couple of weeks
7 later.
8 I'd like to see this run again when we
9 really know how active they are because to my
10 knowledge, it's not even automated yet. And, of
11 course, another piece that's not in any of these is
12 the ability to share data across state lines, and
13 when you make it tougher to get it in one state,
14 then they come visit.
15 Now, then for the three of you, I have a
16 question because it's kind of fun to watch your
17 doctors squirm a little bit when you ask questions
18 about pain pills. And it was like why did you give
19 me 20 Lortab just to get the droopy eyelid fixed,
20 or how much do you normally give your patient when
21 you do a root canal?
22 So we've talked about the obvious huge

1 problems with the holy trinity in Texas and this
2 sort of thing, but do we have another problem with
3 responsible, legitimate physicians who kind of
4 wonder am I giving too much, am I not giving
5 enough? And it's always this, well, I'm going to
6 give him 20 because that way if they get to
7 hurting, at least they'll be all right for a couple
8 of days or four days. And then you get this
9 comment about, well, if they really need more than
10 that, they need to come see me because something is
11 wrong.
12 Do we need to establish some recommended
13 guidelines for the physicians who perhaps are
14 giving out more than they really need to? Which is
15 kind of the other side of the coin of the pain
16 pills -- or the pain clinics.
17 DR. MICHNA: Well, again, certainly
18 education plays a huge role here, But, again, it's
19 individualization of care. So it's knowing your
20 patient, knowing their prior history, knowing their
21 risk factors. Dr. Zacharoff talked about risk
22 assessment and the SOAP and the com.

1 Right now, risk assessment is barely done in
2 the chronic pain setting, but in all reality, I
3 think surgeons or primary care doctors should have
4 a better idea of who they're taking care of. And
5 the fact that they don't even ask questions about
6 prior abuse, misuse, or don't even attempt to get
7 at that information and apply a consistent standard
8 of, as you said, 20 Lortabs or whatever to every
9 patient, that's a problem.
10 We're at the beginning of that process of
11 education. And what we should do is that surgeon
12 should know that I'm dealing with a very high-risk
13 patient; one, maybe I shouldn't be doing the
14 surgery at all if it's an elective kind of thing;
15 and two, if I do it, based on that risk, I'm going
16 to have to change the way I approach his treatment.
17 Instead of seeing him on a post-op visit two weeks
18 later and giving him two weeks of medicine, I might
19 have to see him in two days, and then every other
20 two days. And that's the issue here.
21 We need to individualize the care, and we
22 can't have algorithmic approaches because there's

1 huge variability. There are 80-year-old patients
2 that you assess and, really, the likelihood of
3 misuse or diversion is going to be very low in that
4 population, but others, not so.
5 So how do we mitigate that risk? We change
6 our treatment approach. And, again, this is at its
7 very rudimentary level, particularly in the acute
8 and the perioperative period, but that's where
9 we're going to have to go. And, again, it's
10 education, research, and understanding the
11 individual.
12 DR. MAXWELL: One final comment, I've had
13 three surgeries recently. None of the docs ever
14 asked me about my pain levels or when you had this
15 surgery, what were you on. Do doctors even ask
16 that question? It's one thing to look for the
17 chronic abuser, but do you ask your regular patient
18 when you do a root canal or a small operation? I
19 know but --
20 DR. MICHNA: I'm a specialist in pain. I've
21 done 20 years of work and research in this. I am
22 not the one to ask that question but --

1 DR. MAXWELL: And I think I'm asking it as
2 pointing out another gap.
3 MR. MICHNA: Absolutely, and that's part of
4 the whole problem. Unfortunately, some of the
5 surgeon mentality is I cut and that's it. I don't
6 want to be bothered. And that leads to these
7 excessive prescriptions post-op so I'm not called
8 or bothered. And if they need any more than that,
9 then go see your primary care. That's the bottom
10 line.
11 Again, it's not taking ownership of
12 patients. And this is a larger problem in
13 medicine. But particularly in what you're
14 describing, that particular physician is not taking
15 ownership of that patient.
16 DR. J. WOODS: Thank you.
17 Dr. Kaboli.
18 DR. KABOLI: For Dr. Michna, I have a two-
19 part question for you. The first is more
20 objective, the second more subjective. You made
21 the statement that you thought that the scheduling
22 was a historical error, putting on your hat as a

1 pharmacist. I mean, do you feel like with the
2 Controlled Substances Act, sort of the eight
3 factors, that really it should be a C-II?
4 DR. MICHNA: I think if you asked any of my
5 pain management colleagues or any of us that take
6 an academic approach, there's really no reason why
7 it's not a Schedule II drug. Okay? It isn't.
8 There's no reason. But as I said before, that
9 doesn't mean that it needs to be a Schedule II
10 drug. And we're dealing with a lot of issues as to
11 why it is and what niche it provides in the
12 clinical armamentarium. And that either
13 incentivizes its use or disincentivizes its use.
14 But we have to take, as I said, a higher-
15 level approach here. We're going to have to
16 understand that there's certain reasons why this
17 drug is being used. So unless we address those
18 reasons before we make a dramatic change, I feel
19 that the impact on what we're trying to do, I think
20 we're going to have less an effect on misuse and
21 abuse. And I fear that the balance will be that
22 we'll be affecting more access of care.

1 I mean, look at the data. I mean, the abuse
2 rates in Vicodin, despite the fact it's, what,
3 prescribed 10 times as much, is abused about the
4 same. So that goes to what people are getting the
5 drug, and how it's prescribed, and how it's used.
6 Yes, there's a lot of availability, and that's why
7 it's misused. And eventually, obviously, that's
8 going to be diverted. But given its clinical
9 situation, despite its numbers, it's still -- it's
10 striking that it's not abused more than it is.
11 DR. KABOLI: So I guess you went into my
12 second part that was more subjective. You used the
13 terms "burden" and "inconvenience" quite a few
14 times, and I know somebody else did as well. And
15 there's a lot of things I'm burdened and
16 inconvenienced by. I mean, just flying here, I had
17 to go through security and take my shoes off and my
18 belt and everything. But that's an inconvenience
19 that I'm willing to accept.
20 Fifteen thousand people died last year,
21 according to the CDC, of painkiller-related
22 overdoses. Is making the burden or inconvenience a

1 little bit more, is it worth it in your opinion?
2 This is where it's like --
3 DR. MICHNA: I think it's going to take
4 time, yes. I think, again, we have a huge problem.
5 We're going to have to deal with it. We can't
6 stick our heads in the ground, but how do we
7 approach it? Do we approach it in a feel good
8 manner of just doing something to do it because it
9 makes sense and the hope that something is going to
10 happen, or are we going to take a broader look at
11 the problem and realize this is a multifaceted
12 problem that can't be fixed by one thing or
13 another? And we might cause more problems by these
14 temporary fixes than the --
15 DR. KABOLI: Right, I don't think anybody
16 would argue there's one fix to this. So you're
17 saying, in your opinion, this is not part of the
18 solution.
19 DR. MICHNA: I didn't say it wasn't part of
20 the solution.
21 DR. KABOLI: Oh, okay.
22 DR. MICHNA: I just said that we need to,

1 before we use this as a solution in a combination
2 with many other things, we have to address the
3 issues as to the why doctors feel this is safer,
4 why are they doing it? It's easier for them.
5 Then the fact that we're going to drive
6 healthcare costs up a lot because even if you're
7 willing to it, you're going to have to see your
8 patients more often, which is probably a good
9 thing. But as I said, when you're getting $14 for
10 a follow-up and it costs you $16 to send out a
11 bill, and primary care reimbursements are going to
12 go down, what does that naturally do? It's a
13 disincentive to providing this as an option to your
14 patients. And how great that's going to be and how
15 soon that's going to occur, I don't know. But it's
16 inevitable that's part of what is going to happen.
17 DR. J. WOODS: Thank you.
18 Dr. Suarez-Almazor.
19 DR. SUAREZ-ALMAZOR: Yes. Dr. Lavonas
20 showed a slide that had data or a summary of data
21 from British Columbia, and I had a question
22 actually for all three of the speakers, if anyone

1 could comment, whether there is any international
2 data that has shown whether changes in scheduling,
3 or monitoring plans, or educational strategies have
4 had any impact in abuse or diversion of these
5 drugs.
6 DR. MICHNA: Just in general, you have the
7 California experience, right, where they mandated
8 continuing education and pain management after the
9 famous case there. And then 10 years later, they
10 looked at the impact. Just providing education
11 doesn't necessarily mean you're going to have an
12 impact. It's how you provide it and the systems,
13 as Dr. Zacharoff was speaking about.
14 So just requiring somebody to do continuing
15 education or to have their colleagues give them the
16 answers that they took on a computer thing is not
17 the solution here. This is a more global problem
18 than that.
19 DR. SUAREZ-ALMAZOR: Yes, but I was
20 wondering other strategies as well. What have
21 other countries done and whether there has been a
22 change or not. And I don't know. Have there been

1 other programs with respect to policy that have
2 resulted in any changes in use?
3 DR. LAVONAS: I agree. I'm not aware of
4 specific international programs that would be
5 applicable to this question. It would also be
6 tough because I think one thing that we're not
7 going to fix today is the American healthcare
8 program.
9 The American healthcare system has enormous
10 challenges with access for a large, large
11 proportion of Americans. So that makes each one of
12 these decisions -- if you're starting to go down
13 the wrong path, it's patients in our system will
14 get further down the wrong path before an
15 intervention can come to get them recorrected than
16 would be the case in a country where healthcare is
17 more responsive. And we're not going to fix that.
18 It's the landscape we have to deal with.
19 But in terms of whether making hydrocodone
20 less accessible in a system than other drugs, I'm
21 not aware of any international studies that have
22 looked at that.

1 DR. J. WOODS: Thank you.
2 Ms. Moore.
3 MS. MOORE: I just wanted to make two points
4 of clarification. Previously we were -- I'm not an
5 expert on nurse practitioner laws, but on physician
6 assistant laws, there are 15 states where PAs
7 cannot write Schedule II. And in places like where
8 I'm from, from Texas, there's a lot of rural areas,
9 and the physician is only onsite once every 10
10 days. So that would really be a barrier to care if
11 it was a Schedule II.
12 Also, recently, within the last six months,
13 the prescription monitoring program has gone
14 online, and physicians, PAs, and I'm assuming nurse
15 practitioners can log into it after they're
16 registered.
17 DR. J. WOODS: Dr. Nelson.
18 DR. NELSON: Thank you.
19 I guess this is probably for Dr. Zacharoff,
20 but maybe anybody might want to answer it. But you
21 had made some comments, and actually, some of the
22 others that had spoken kind of echoed some of the

1 comments, the three of you there. But I think
2 there's not a specialty on earth that doesn't think
3 that their discipline is under-taught in medical
4 school, and I can promise that.
5 I do agree that pain medicine and opioid
6 pharmacology, et cetera, is not well taught in the
7 classroom. It's probably a better subject to teach
8 in the clinical environment anyway, where you can
9 actually see a patient and learn how pain presents
10 and how pain should be managed and all. And often
11 it's taken a little bit out of context -- it's in a
12 classroom -- so contextualizing it in a clinical
13 environment might help.
14 It's hard to imagine that there are
15 physicians out there, just by walking on the earth
16 and by watching television and reading newspapers,
17 don't know that this is problem that's going out
18 right now. So those that claim that they never
19 knew that there were problems with prescriptions
20 opioids, you kind of wonder how connected they
21 really are.
22 The role of education, as you pointed out,

1 is pretty limited. And there's nobody that's going
2 to argue against education. I mean, clearly, it's
3 the baseline to do everything. But I guess where
4 I'm going with my question is since CME programs
5 don't work very well and since guidelines are not
6 very well utilized, and has been pointed out, the
7 California mandate didn't work very well, what do
8 you see the role of a pretty strict short-acting
9 opioid REMS program in trying to prevent some of
10 these overuses?
11 In other words, we have a long-acting opioid
12 REMS, which is now mandatory, but we could have
13 something similar for short-acting opioids, which
14 seems to me like it would be valuable. It'd be
15 hard to implement. There'd be a million issues
16 with it, but if done properly, it could guarantee
17 that every physician or every healthcare provider
18 that uses opioids is up to date in a mandatory way.
19 Remember, this is the same thing we talk
20 about with seatbelts. Until you institute the
21 click-it or ticket, nobody is going to wear their
22 seatbelts. And suddenly when it becomes a rule and

1 not just a thought, it becomes more utilized. And
2 I guess along that same line, what is wrong with
3 guidelines that are a little bit dictatorial?
4 Instead of just saying here's some good fluff that
5 we all think would be good to know, instead say
6 this is the way you're supposed to do it. Some
7 groups like the dentists have been fairly proactive
8 in some of these rules.
9 DR. ZACHAROFF: To answer your first
10 comment, I agree with you. Back when the opioid
11 REMS advisory committee meetings were taking place,
12 I was sitting in the audience, and I was actually
13 thinking exactly what you said; could some
14 mandatory implementation of education with respect
15 to the immediate release short-acting opioids force
16 the issue?
17 Personally, I think it could. However, a
18 lot of arguments were made that it might severely
19 restrict access. But personally, I think the
20 answer is yes.
21 With respect to the second point you brought
22 up, I was actually thinking about this, this

1 morning, because the seatbelt analogy is a really
2 good one. My daughter is 22 years old. She was
3 brought up in the age of the seatbelt, and she
4 buckles up before the car starts moving. I drive
5 around, and I see a load of people her age texting
6 while driving. And what it makes me wonder is
7 could education just solve the whole problem? We
8 decrease the number of fatalities as a result of
9 seatbelts for sure, but now every other week it
10 seems I read about the dangers of texting and
11 driving and accidents that were caused by that.
12 So I guess my last statement would be what I
13 would reinforce. I think in the absence of a
14 foundational education, then continuing education
15 is only going to make a dent. There are a number
16 of things that we could do for students and even
17 residents and fellows in training, whether it's
18 standardized patient, whether it's some period of
19 time where residents are mentored by an attending
20 who really understands what they should do. There
21 was a recent study that was actually done where
22 they looked at residents and fellows who were

1 prescribing opioids, and they compared that in the
2 same institution to attendings. And what they
3 found was that residents and fellows were twice as
4 likely to prescribe an opioid for someone with the
5 same exact level of pain.
6 What I think is missing in this whole
7 discussion is the fact that there is so much that
8 needs to take place before the patient's ever being
9 considered to be a candidate for opioids, and
10 that's the place where the educational vacuum is.
11 I always refer to it as patient has been determined
12 to be an appropriate candidate for opioid therapy.
13 There's a lot that happens before you get to that
14 point, and it seems like we're just talking about
15 what happens once you reach that point. There's no
16 education leading the healthcare providers to get
17 to that point.
18 DR. J. WOODS: Thank you. Dr. McNicholas.
19 DR. MCNICHOLAS: Thank you because that was
20 a beautiful lead-in to my question, and that is, is
21 there evidence for what patients are offered,
22 provided, et cetera, before we get to this

1 prescription for opioids? And I'm not talking
2 about a broken wrist or something like that, but
3 the patient who comes in with my knee hurts and
4 I've got arthritis and I need opiates.
5 Is there any standard, and is that standard
6 utilized? And we have two pain experts standing up
7 there, so I was going to ask the question.
8 DR. MICHNA: Well, certainly, there was the
9 WHO pyramid starting with nonsteroidals and weak
10 opioids and full opioids, but that's kind of a
11 naive approach to pain and really is -- again, it
12 has to do with the individual situation.
13 The problem is when in a primary care
14 situation, you're dealing -- you have five minutes
15 to see a patient. The patient's that complaining,
16 you can see where the forces of a situation might
17 lead you to take an easy way out. And I think
18 certainly there's a lot of primary cares, based on
19 those practice limitations and needs, who take the
20 easy way out and go right to the opioid, based on
21 patient demands or whatever.
22 Pain takes time for evaluation, and you need

1 to spend time with the patients. But when you're
2 not paid for it and you don't have the time to do
3 it, this is where some of these problems start
4 occurring.
5 DR. MCNICHOLAS: But is that something that
6 the overarching healthcare system needs to look at,
7 is both reimbursement for appropriate assessment,
8 reimbursement for appropriate referrals,
9 reimbursement to the patient for following up with
10 that physical therapy or whatever is being
11 recommended before you get to we need to start
12 Percocets?
13 DR. MICHNA: Right. And that's part of the
14 problem is that we are not -- it's what you
15 incentivize is what happens, right? So you
16 incentivize doing cataracts, and everybody has
17 cataracts. You incentivize doing laminectomies,
18 and everybody -- the United States has 50 percent
19 of the laminectomies in the world. You incentivize
20 doing fusions then, so nobody does lamies anymore.
21 Now everybody's getting lumbar fusions.
22 What you incentivize in terms of physician

1 and practitioner behavior is what is going to be
2 accomplished. And right now, we are
3 disincentivizing ownership of patients, taking time
4 with the patients, and really dealing with all
5 these issues that -- again, the more we've done
6 research on it, the more we understand that there
7 is evaluation processes that have to go on to
8 mitigate risk and therefore diversion and other
9 issues. And unless we incentivize that, again, in
10 the ivory tower, I can pontificate all I want about
11 what I think needs to be done, but the primary care
12 is going to turn to me, okay, I have two minutes to
13 see the patient. How am I going to do all this?
14 DR. J. WOODS: Thank you. Ms. Phillips.
15 MS. PHILLIPS: I know we've been talking
16 about pain management all afternoon, but taking the
17 advantage of having Dr. Lavonas up there, I have a
18 question about the cough products with hydrocodone.
19 And the data that I looked at seem to indicate that
20 there was a fairly low rate of abuse, and is that
21 borne out in what you see in your data as well? Or
22 is that another problem that we're not looking at

1 because the issue of combination products for
2 analgesia is so much larger?
3 DR. LAVONAS: I'm not sure that I heard your
4 whole question, so I want to state it back to you
5 and then you can correct me if I heard you wrong.
6 So are you asking if we're observing abuse issues
7 with the hydrocodone antitussive products?
8 MS. PHILLIPS: Right.
9 DR. LAVONAS: I have had that happen in the
10 past. In fact, it was the first time I was a
11 victim of prescription fraud was about one of those
12 products. My assistant, who didn't actually exist,
13 was calling in prescriptions all over town.
14 But honestly, in the last 15 years, I don't
15 think I have. I'm not sure whether the drugs are
16 just too constipating or too sedating, or people
17 prefer others. But personally, I haven't seen a
18 case in easily a decade. And the data really show
19 that these are mostly the analgesic preparations
20 that get down to these various spectrums of
21 diversion and abuse much more so than the
22 antitussives, perhaps.

1 DR. J. WOODS: Thank you. I think we're to
2 Dr. Lorenz.
3 DR. LORENZ: Thank you.
4 I was quite interested in the question of
5 incentives. And, in particular, on the seatbelt
6 analogy, my own motivation, I have to admit, often
7 relates to the ticket, not to the education I had
8 about the seatbelt, which unfortunately, I usually
9 know and sometimes ignore.
10 The other issue with the seatbelt analogy is
11 that you know exactly what process is involved in
12 improving it. You have to snap it usually, that
13 little thing on your left, or right, depending on
14 where you're sitting. And that brings me to the
15 question of quality measurement.
16 So one of the things that's notable, of
17 course, is the way that Medicare in particular is
18 moving towards quality measurement as a form of
19 incentive. And it makes me wonder what incentives
20 would be most appropriate in terms of incentivizing
21 better opioid prescribing, both what settings and
22 what types of measures. And, in fact, whether

1 that's a policy lever for FDA to improve this
2 issue.
3 DR. LAVONAS: So I'll take one stab at that.
4 So I'm going to put on my pharmacy and therapeutics
5 committee chair hat here. So working at Denver
6 Health, we are big fans of lean process improvement
7 in standard work, and we have a multidisciplinary
8 team within primary care, primarily or led through
9 primary care, to look specifically at creating
10 standard work around opioid prescribing. That's
11 not fully rolled out yet. But what we found with
12 other conditions with quality initiatives in
13 primary care is, frankly, doctors are a competitive
14 group, and if you give them a scorecard, they'll
15 move to improve.
16 So our diabetes medication, our diabetes
17 control, and our lipid goals, and our hypertension
18 goals all improved markedly when we simply provided
19 doctors feedback to their performance versus their
20 peers in the same clinic and their peers in the
21 system. So I don't think it takes a big stick, but
22 it does take data.

1 DR. ZACHAROFF: And I would add that I think
2 that that's exactly what the Joint Commission is
3 trying to do with their set of recommendations in
4 the sentinel alert. But it's going to be a slow
5 go, and it may very well be the ticket before it
6 becomes the habit of good practice.
7 DR. J. WOODS: Thank you. One final
8 question from Dr. Kaboli.
9 DR. KABOLI: Actually, it's just a quick
10 comment. Dr. Michna, I don't know if you're trying
11 to be hyperbolic, but in primary care, they don't
12 have two to five minutes. I mean, maybe at the
13 Brigham, they have to see 30 patients an hour, but
14 in primary care, -- I work with primary care docs.
15 We don't see that many patients in an hour. So I
16 think it's a little bit of an excuse. The same
17 with the Affordable Care Act, actually,
18 reimbursement for primary care is going to go up.
19 So I understand your point, but I don't
20 think that's an excuse that physicians should be
21 able to say, well, I don't have time to spend with
22 my patients, so I will give them prescriptions.

1 That's my opinion.

2 **Committee Questions (continued)**

3 DR. J. WOODS: I want to thank you folks.
4 This was a very good discussion, and it provides a
5 great intellectual context for us to make a
6 difficult decision.

7 Now, I want to go back to those questions
8 that we forgot about before lunch. And for those
9 of you who can remember what the questions were and
10 who you were, we'll start with Dr. Olbrisch.

11 DR. OLBRISCH: I'd like to know if we have a
12 real answer to the question of whether
13 acetaminophen really makes a difference in the
14 abuse potential of hydrocodone. And I think I
15 heard some contradictory answers to this question
16 in some of the presentations this morning. So do
17 we have an answer to that question?

18 Also, a follow-up on that is I believe the
19 FDA reduced the amount of acetaminophen that could
20 be included because of the potential for patients
21 to overdose on acetaminophen with confusing
22 labeling. So wouldn't that also make a difference

1 in terms of the data that's available for what
2 patients may be doing with it if, in fact, it does
3 make a difference given lower amounts of it?
4 Can anyone answer that question?
5 DR. STAFFA: This is Judy Staffa. For the
6 first part of your question, I think, Dr. Dormitzer
7 presented what we know about the question about
8 whether adding acetaminophen changes abuse. Again,
9 given that there's no single ingredient on the
10 product, on the market at this time, we don't have
11 direct comparisons. All we can do is look at the
12 crude abuse ratios in other product areas with
13 single-ingredient oxycodone versus combination, and
14 again with tramadol, and again, we see lower abuse.
15 But we have no statistical measurements on that.
16 So it's still an unanswered question, but the data
17 we have suggests that maybe adding the
18 acetaminophen does decrease the abuse.
19 With regard to talking about the actions the
20 agency is taking on acetaminophen, I can
21 ask -- Dr. Mary Willy is here who could address
22 that issue.

1 DR. WILLY: Good afternoon. Yes, in January
2 of 2011, the agency did ask manufacturers to drop
3 the dose of acetaminophen in combination products
4 to 325, but companies have been given a period of
5 time to make that change. So it hasn't been
6 actually implemented, so we can't provide any data
7 for you, for that question.
8 DR. OLBRISCH: Thank you.
9 DR. J. WOODS: It's a very good question,
10 and I think an important one.
11 Anyone else want to take a shot at it? It's
12 one of the things we don't have quite enough
13 information on, I'm afraid, at least that's my take
14 on it.
15 Dr. Bagiella.
16 DR. BAGIELLA: I'm going back to the
17 denominators, and so I have a question for
18 Dr. Dormitzer on her slide 23. In that table where
19 you considered the relationship between the number
20 of tablets and the kilograms, I was wondering
21 whether or not you estimated from the kilograms
22 that you have available the number of tablets that

1 would be used, and used that as your denominator
2 rather than the number of tablets prescribed to
3 account for what is lost in the distribution chain.
4 DR. DORMITZER: I guess I need a little bit
5 more clarification. As far as what's lost in the
6 distribution chain, that -- let me think about
7 this. That's not -- well, it's sort of included
8 when you're just looking at -- well, these are
9 the -- DEA is providing the number of kilograms
10 sold right down to retail level.
11 DR. BAGIELLA: Right, but you're -- and
12 that's their denominator, right?
13 DR. DORMITZER: That's their denominator.
14 DR. BAGIELLA: Right. And your denominator
15 is the number of tablets prescribed, right?
16 DR. DORMITZER: Yes.
17 DR. BAGIELLA: And you said there is a
18 problem with that because your denominator does not
19 account for what is lost in the chain, and their
20 denominator does not account for the actual number
21 of tablets. And I was wondering since you have
22 this conversion table there, whether you can

1 estimate the number of tablets that go down the
2 chain --
3 DR. DORMITZER: No.
4 DR. BAGIELLA: -- and use that as your
5 denominator.
6 DR. DORMITZER: Right. No, no. You can't.
7 Basically, this was -- how we derived the number of
8 tablets per kilo really was a weighted average of
9 the number of milligrams per tablet, and we also
10 knew that, okay, well, this is how many tablets are
11 dispensed across the different prescribing ranges.
12 And so it's a weighted average. And so that's how
13 we derived this, was how many tablets does
14 each -- or how many exposure opportunities does
15 each kilogram represent.
16 So that's not assuming -- that's just the
17 number of tablets per kilogram. So the lost in
18 supply chain is completely taken out of this. And
19 there isn't really a way to put it back in.
20 Probably I would say -- and this is where I'm not a
21 law enforcement person, so I can't say. But what
22 about looking at the slide of -- the one that I

1 just brought over about how -- the NSDUH slide?
2 I e-mailed this slide. This is from the
3 National Survey on Drug Use and Health, and what
4 you can see is, well, what is the proportion of
5 people -- now, these are people who reported non-
6 medical use of pain relievers.
7 So this includes all pain relievers. And,
8 basically, what we found was that right at the very
9 beginning, 55 percent got it for free from a friend
10 or a relative. Only, I don't know, 10 percent got
11 it through nefarious sources, I mean, the Internet,
12 a drug dealer or other. That's roughly 10 percent
13 that were getting it through not a prescription. I
14 mean, just because they got it from a -- the
15 prescription may or may not have been legitimate,
16 but 55 percent got it free from a friend or a
17 relative. But that friend or relative, 80 percent
18 was from one doctor.
19 So most of the non-medical use did derive
20 from prescriptions. Whether they were legitimate
21 or not legitimate, we have no idea. So it's not
22 really showing that there's a lot that I would say

1 is due to lost in the supply chain, but that would
2 be, I'm guessing, the drug dealer stranger. I'm
3 guessing some of them are prescriptions, but many
4 of them are not. Bought on the Internet and other,
5 that's roughly 5, 9 -- yes, so that's 9 percent.
6 So it's roughly 10 percent.
7 Does that answer things? Sort of.
8 DR. J. WOODS: Thank you. Dr. Nelson. No?
9 Dr. Lorenz, do you remember your question?
10 DR. LORENZ: Yes. Thank you.
11 I was remembering back to the labor action
12 in the NFL in the fall and how upset Americans were
13 the umpires didn't seem to be able to do their job
14 very well. But it's shocking to me that we still
15 deal with inadequate epidemiologic data to compare
16 some of these issues from time to time. And it's
17 shocking that Americans put up with inadequate
18 umpiring in that regard, not due to the fault of
19 the agencies at hand. And at the same time, it
20 begs the question for me of how we're going to
21 monitor this issue over time.
22 So when I was hearing these different

1 perspectives, I find it troubling that we argue
2 both about the substantive conceptual issues and
3 the data quality. But it also begs the issue of
4 what we're going to do differently going forward,
5 and in particular, where there's so much
6 uncertainty about policy, what the standard for
7 success should be.
8 So I wanted to pose the issue to the DEA
9 speaker, as well as the FDA, to see if there's any
10 concurrence on how to address those issues going
11 forward.
12 DR. STAFFA: This is Judy Staffa. I would
13 just like to thank you for pointing out the
14 inadequacy of the data because we would love to
15 have better data. Thank you for putting it in the
16 record.
17 DR. J. WOODS: We have a more general
18 question about electronic prescriptions left over
19 from this morning, we think. DEA was going to
20 check into it with respect to C-II schedule drugs,
21 I think. Do we have that wrong?
22 MR. RANNAZZISI: If you guys will go to our

1 website --
2 DR. J. WOODS: Turn your mic on. Would you
3 turn your mic on?
4 MR. RANNAZZISI: There's an interim rule
5 that allows you to do Schedule II through V
6 controlled substances for your electronic
7 prescribing. If you go to our website, it's
8 interim rule with further questions concerning
9 electronic prescribing in controlled substances.
10 But because it's an interim rule, you're
11 allowed to do it as long as you are using a vendor
12 that's got a system that meets the security
13 requirements to electronically prescribe. So there
14 should be no problem. We haven't retracted that
15 rule. It's still a rule that's on the books. An
16 interim rule can stay in effect for a while until
17 it goes final, and so there's -- now, if your state
18 doesn't allow it -- obviously, a state law that's
19 more restrictive trumps the federal law. State law
20 could be more restrictive. It can't be less
21 restrictive.
22 As far as the other question, again, we're

1 acting on a petition. The petition was very
2 straightforward. When we gather all our
3 information and send it to HHS, it's the
4 information we have available. Is the information
5 perfect? Absolutely not, but it's the best we have
6 at the time. And we'd like to have better
7 information, but I can only give you what I have.
8 DR. LORENZ: I certainly respect that.
9 Thank you. My only concern is that we might use
10 reduction in hydrocodone dispensing as -- or even
11 adverse events from hydrocodone as the measure of
12 success here, and I don't know that that's the
13 right answer. It seems like we're playing a bit of
14 a Whac-A-Mole game.
15 MR. RANNAZZISI: The other question we had
16 when I looked at the National Survey data -- and
17 it's true. They say oh, well, 80 percent got it
18 from at least a person who got it from one doctor.
19 But the question is, who is that doctor? And it
20 depends on how the question's asked. Is that
21 doctor an Internet doctor? Is that doctor a pain
22 clinic doctor? A rogue pain clinic doctor? Is it

1 a doctor that's in a practice that generally
2 doesn't prescribe but is moonlighting to make extra
3 money?
4 You can't have a very, very specific
5 question because it kind of destroys -- if the
6 survey gets way too specific, it destroys the
7 survey. But in the same token, you've got to give
8 them some leading questions to try and flush out
9 who this doctor is. And prior to the Internet, we
10 didn't even ask about the Internet. I think that
11 was a tag-on in 2005 or 2006.
12 DR. J. WOODS: Thank you. Dr. Nelson.
13 DR. NELSON: Thank you. I actually
14 remembered my questions. One of them was for
15 Dr. Dormitzer, and it had to do a little bit with,
16 I think, her slide number 28, which is what got me
17 to think about it.
18 But the ultimate question is how do
19 you -- and it was just because it was a pretty
20 slide to look at, I think, and it kind of -- it
21 says it. It says it all. How do you account for
22 the fact that hydrocodone and oxycodone are not

1 necessarily used in the same patient population for
2 the same indications when you're trying to
3 determine the denominator of million tablets
4 dispensed?
5 In other words, if, for example, the abuse
6 potential was equal between the two and hydrocodone
7 was used a little bit more like the workhorse agent
8 and given out a lot more liberally to perhaps to
9 people with much less of an abuse potential, it
10 would make the drug look better when you looked at
11 the number of pills data; is that right? Because
12 you'd be giving it to so many more people who were
13 not at risk. It's the forest for the trees or the
14 Pollyanna phenomenon.
15 Does that make sense? Did you do a count
16 for that? Am I not explaining myself?
17 DR. DORMITZER: I'm guess I'm trying to
18 understand it. This is about number of pills --
19 DR. NELSON: Dispensed.
20 DR. DORMITZER: Number of tablets dispensed.
21 DR. NELSON: Right. So if they just make
22 believe they have the same abuse potential, and

1 you're giving out so many more hydrocodone pills
2 for much weaker indications to many more people who
3 are much less likely to abuse it, when you distill
4 it down to number of tablets dispensed, so the
5 denominator, don't you then -- because so many
6 people are not a risk, you'll find that those pills
7 look safer from an abuse perspective.
8 DR. STAFFA: This is Judy Staffa. I can try
9 to help here. I think that was the logic we were
10 using when we were trying to use tablets dispensed
11 for the oxycodone combination products in the
12 denominator when we could get a numerator that was
13 associated with that, because our prescribing data
14 tells us that that's at least closer an indication
15 in clinical use than the single-ingredient
16 oxycodone. And that's where we end up with only
17 using the DAWN data because that's the only place
18 we can tease apart the numerator as well.
19 But you're right. It's not a perfect
20 comparison. There's still unaccounted for
21 differences even when we do that, but we just
22 didn't know what else to compare it to. I think as

1 was said, there's not really an equal clinical
2 comparator that would get at that same denominator
3 that would be comparable for the hydrocodone. So I
4 think your concern is a good one.
5 DR. DORMITZER: And then each tablet is the
6 exposure opportunity, and how it goes from -- I
7 mean, I think a lot of people have leftover Vicodin
8 in their medicine cabinet. And so this is sort of
9 adjusting to take into account that there are
10 leftovers as well. But it is seeing each pill as
11 the exposure opportunity rather than, I don't know,
12 each bottle of tablets, or each patient who may
13 get, I don't know, 12 prescriptions. Every person
14 is going to be different amount.
15 DR. NELSON: I'm just afraid we're comparing
16 a little bit of apples and oranges, because since
17 hydrocodone is Schedule III, it's much more
18 liberally dispensed, prescribed, I think.
19 DR. DORMITZER: Well, that's why we were
20 trying to see what are the differences. I mean,
21 yes, it's 130 million prescriptions.
22 DR. NELSON: So there's a different

1 population of patients.
2 DR. DORMITZER: Yes.
3 DR. NELSON: Yes, that is the point. So
4 that's why it's not necessarily easy to compare the
5 two.
6 DR. DORMITZER: Right. This is, I guess,
7 trying to broaden our perspective on who is the
8 population at risk.
9 DR. NELSON: Okay.
10 DR. DORMITZER: So it's not just the person
11 receiving the prescriptions. It goes way beyond
12 that.
13 DR. NELSON: Okay. Can I ask one more
14 question to the gentleman from the DEA or perhaps
15 somebody else? But we saw a lot of data trying to
16 look at the 15-milligram cutoff dose when we're
17 trying to determine whether or not the drug
18 hydrocodone should move from Schedule III to
19 Schedule II.
20 But the wording of the scheduling isn't
21 really whether therapeutic use produces dependence
22 and addiction, it's whether abuse does, right? So

1 just from the wording perspective, the DEA goes, we
2 again might be looking at the wrong issue, right?
3 We really should be looking not at what therapeutic
4 doses do, but what abuse doses do. And I don't
5 know that there's data out there for that.
6 But I don't know if this factors into the
7 decision making of DEA or not because we have to be
8 looking at abuse, not high therapeutic use, which
9 is what all the addiction studies more or less have
10 looked at. Maybe that's just a comment.
11 DR. J. WOODS: Dr. Mendelson, do you have a
12 question?
13 DR. MENDELSON: From this morning or from
14 just the few minutes ago? I had a comment more for
15 the speakers who just completed. But if people
16 aren't going to the prescription drug monitoring
17 programs to survey them, maybe what we ought to do
18 is -- and I think this might even be something the
19 agency or the DEA could actually mandate -- send
20 the information back to the doctors, right?
21 Every time someone prescribes, send them a
22 report. Every time -- you could do it daily,

1 weekly or monthly. But then you would weed out
2 more of those patients who aren't your patients who
3 are getting opiates, and you could see what
4 patients are getting, see if other physicians have
5 prescribed.
6 Yet if people won't log into prescription
7 monitoring programs, send them the information.
8 You have the data. Push it back out to them the
9 other direction.
10 DR. J. WOODS: I want to remind people that
11 we're still trying simply to clarify things, not
12 have a general discussion, but I turn the floor
13 over to Dr. Throckmorton now.
14 DR. THROCKMORTON: I actually had a comment
15 for Dr. Lorenz. It was less a turning over.
16 Dr. Throckmorton, FDA.
17 So, Dr. Lorenz, you'll be given an
18 opportunity tomorrow to talk about things like how
19 we might measure the impact of your
20 recommendations. And I for one would be delighted
21 to hear some other ways of measuring success other
22 than just simply kilos of drug dispensed. I think

1 it's important to look at aspects of access, for
2 instance, and things like that. But how to do that
3 is devilishly challenging, so look forward to your
4 comment.
5 DR. J. WOODS: Dr. Suarez.
6 DR. SUAREZ-ALMAZOR: I'd like to go to the
7 FDA slide 33, which is the one that says "no data
8 to support DEA assertion adding acetaminophen to
9 hydrocodone does not deter abuse" to get an -- 33.
10 It was the last speaker.
11 DR. DORMITZER: This is about does -- yes.
12 DR. SUAREZ-ALMAZOR: Yes, this is the one.
13 Yes. I was wondering if I could get some
14 clarification. It seems to me that this is based
15 on the number of tablets. However, the dosages are
16 really very different.
17 So the potential for emergency department
18 visits would be much more with single drug
19 preparation just because of the nature of the
20 dosing, per se. I mean, I don't know if you can
21 control for that or not, but I looked for tramadol
22 as well. And tramadol, when you look at the

1 combination, it's only 37.5 milligrams compared to
2 50 and above for the single drug preparation. And
3 if you look at oxycodone, the maximum for the
4 combination is 10, but you can get up to 80 with a
5 single drug. So that on its own would cause more
6 emergency department visits. So it seems to me
7 that this is a little biased as far as interpreting
8 the data this way.
9 DR. DORMITZER: This was just an indirect
10 analysis because since hydrocodone does not have
11 single-ingredient and combination products, so we
12 can do a direct analysis, we had to look at other
13 opiates that had single and combination products.
14 With this one, it was the number of abuse-
15 related emergency room visits for oxycodone IR
16 products, not all single ingredients, just the IR
17 single ingredient. And then the combination
18 products are already IR. Because I was trying to
19 get at apples and apples as much as I could, or I
20 don't know, at least both fruit.
21 So that's what I was looking at. And then I
22 did use as my denominator a number of extended

1 units. And, yes, it's very possible that the
2 number of people entering the emergency room for
3 the single-ingredient products are receiving a
4 higher milligram strength. That's entirely
5 possible.
6 But the question was with the addition of
7 acetaminophen, what are the abuse rates that we're
8 seeing. And they do appear to be lower than the
9 single ingredient, and that could be the result of
10 lower milligram strength. That's entirely
11 possible.
12 It's also possible that there are other
13 reasons as well, such as they're not injecting,
14 they're not snorting. I don't know, they didn't
15 take as much. There are lots of -- I could go on
16 for a long time about what are the possible
17 different reasons.
18 So I don't know that. But, yes, one of the
19 possible explanations of why the single ingredient
20 is higher is that they were the patients that were
21 abusing higher milligram strength opiates. But
22 these are abuse-related ED visits. This is not

1 just ongoing because you were having problems with
2 a drug that you were using legitimately.
3 DR. STAFFA: This is Judy Staffa. I just
4 want to clarify one point on that. I think it's
5 difficult to tease out because the reason you add
6 the acetaminophen is to lower the dose of the
7 opiate. You're looking for the synergy between the
8 two. So there aren't high dosage formulations with
9 acetaminophen in them for us to be able to do that
10 kind of more sensible comparison, but it's not a
11 clinical -- it doesn't make sense clinically.
12 DR. DORMITZER: It's entirely possible that
13 they have lower milligram strength. But this is
14 the best we could come up with as far as comparing
15 it to -- hydrocodone, there are all low milligram
16 strength combination products. And that is
17 probably why it's abused less.
18 DR. J. WOODS: I'm going to you let in on a
19 secret. We're five questions away from a break.
20 Dr. Jones.
21 DR. JONES: So, Cathy, you could probably
22 stay up there because this is going to be for you.

1 I have two questions. The first is sort of just a
2 general question, I guess a little bit of what
3 Dr. Nelson asked.
4 So based on the criteria for different
5 schedules, so Schedule III is moderate to low
6 physical dependence or high psychological
7 dependence, and then it's severe for physical and
8 psychological for Schedule II. So if hydrocodone
9 as a single ingredient is a Schedule II, how can we
10 say that a combination -- if you're not basing it
11 just on medical use but non-medical use or
12 abuse -- has any difference for physical dependence
13 or psychological dependence? I'm unclear of how
14 that distinction is made.
15 DR. DORMITZER: Silvia?
16 DR. CALDERON: When Congress enacted the
17 Controlled Substances Act, Congress decided to
18 place hydrocodone single entity into Schedule II
19 and the combination products into Schedule III.
20 And that's where they sit today. And so I think
21 the question you're asking goes to why we're all
22 here today. So, I mean, that partially answers

1 your question.
2 DR. JONES: So legislatively, it was --
3 DR. CALDERON: It was done legislatively,
4 yes.
5 DR. JONES: And then my second question also
6 gets to something that Dr. Nelson brought up, and
7 it has to do with the denominator of extended
8 units. I can understand not wanting to use
9 kilograms. Maybe looking at morphine milligram
10 equivalents would be another denominator that you
11 could look at. But if you do extended units, I
12 wonder if it's not worth putting some sort of
13 inflation factor for oxycodone because your
14 previous slide had about a 1 to 1.5 conversion
15 factor when you compared it to morphine.
16 So if you multiplied the tablets, that would
17 represent that one tablet of a combination product,
18 whether it's 5 or 10 of Percocet or 5 or 10 of
19 Vicodin, the amount of oxycodone would be slightly
20 more powerful. So if you added some inflation
21 factor of 1.5, I think your denominators would
22 level out a little bit, or your ratios would level

1 out a little bit. And it might be more appropriate
2 to look at it in that manner, because from a
3 mortality perspective, I wouldn't necessarily say
4 that they're equivalent.
5 DR. DORMITZER: I guess my objection is
6 having an inflation factor because the whole point
7 is evaluating the abuse potential of each milligram
8 or how it is dispensed. I mean, fentanyl --
9 10 milligrams of fentanyl is so over the top more
10 potent than 10 milligrams of hydrocodone. One is a
11 standard dose, and the other one would be a fatal
12 dose.
13 So I actually don't want to adjust for
14 morphine equivalent. I want to do the opposite
15 because I'm trying to differentiate between these
16 different drug products based on how they are
17 prescribed. So that's why I want to use the
18 extended units or the number of tablets because
19 each one is an exposure.
20 DR. JONES: But they have the
21 potential -- from a morbidity or mortality
22 perspective, they have the potential to cause more

1 damage if it's a stronger product. Even if it's
2 one product of each, if one person had a fentanyl
3 lozenge versus a Vicodin tablet --
4 DR. DORMITZER: Exactly.
5 DR. JONES: -- that one fentanyl lozenge
6 will be more dangerous. But you're saying that
7 oxycodone in combination and hydrocodone in
8 combination are equivalent, but when you look at
9 morphine in milligram equivalents, they are not.
10 DR. DORMITZER: I'm just looking at the
11 epidemiology of the abuse. I was not looking at it
12 from that perspective. So it was just examining
13 how many emergency room or -- the number of
14 emergency room visits per million tablets
15 dispensed. And even like that, oxycodone was
16 somewhat higher.
17 So now I'm just looking at the combinations,
18 and I am seeing somewhat higher. But the
19 single-ingredient, high milligram strength tablets,
20 or prescriptions, do represent more risk for abuse.
21 Well, actually, it's more risk for abuse, more
22 medical events associated with that abuse, because

1 we don't know how many people are taking Vicodin
2 and falling asleep and waking up and never having a
3 problem again.
4 So we're not measuring that. We're talking
5 about medical events. So these are, I don't know,
6 the serious side of drug abuse.
7 DR. JONES: And have you looked at the
8 ability to see within the DAWN ED data single drug
9 injections or how many of these hydrocodone also
10 had oxycodone?
11 DR. DORMITZER: Most, both -- this is true
12 for oxycodone and for hydrocodone. The
13 overwhelming majority had more than one drug
14 onboard. And it's entirely possible that they had
15 hydrocodone and oxycodone onboard, and so then they
16 would be in both numerators.
17 DR. JONES: So is it possible to do single?
18 DR. DORMITZER: But if I did it like that,
19 then I would not have data. What I do know is that
20 the proportion of emergency room visits that were
21 the result of a single drug is higher for oxycodone
22 than hydrocodone, but that's it. And so, no, I

1 can't -- we don't have that level of detail. I
2 mean, we -- the data just aren't -- they're not
3 that precise. But the overwhelming majority, if
4 you wind up in the emergency room, the likelihood
5 that you had more than one drug onboard is high.
6 DR. JONES: Okay.
7 DR. J. WOODS: Four to go. Ms. Chambers.
8 MS. CHAMBERS: Thank you.
9 I'm wondering if we are looking at two
10 different populations, and I wonder if anybody that
11 we've listened to has an answer. We're talking
12 about acute pain and chronic pain, and I know that
13 for chronic pain, there are 100 million people
14 living with chronic pain. And perhaps thinking
15 141 million prescriptions for a hydrocodone
16 product, how many of these are being prescribed for
17 acute pain, and how many are being prescribed for
18 breakthrough pain and chronic pain? Because maybe
19 we need to look at these two different populations
20 and consider how to help each population better.
21 And I wondered if maybe Dr. Michna or somebody
22 might have an answer to help us know the difference

1 between that.
2 DR. J. WOODS: We have a taker.
3 DR. MICHNA: I don't know what the exact
4 numbers are, but certainly, most opioids are
5 prescribed for short periods of time and for acute
6 pain for the majority. But the relative Vicodin
7 versus oxycodone, hydrocodone, I don't know.
8 MS. CHAMBERS: Thank you.
9 Specifically, I'm thinking about the
10 education. And you were talking about education,
11 and we're talking about literally the prescribing.
12 And then we sort of talked -- you sort of talked a
13 little bit about alternatives to that. And you
14 mentioned the WHO scale and starting down low. And
15 then you kind of backed up and said, well, there
16 are other things.
17 As I've been trying to find research to help
18 people with other ideas on how to manage their
19 pain, I find precious little. And I'm hoping that
20 this is something maybe we can be thinking about or
21 maybe you can give us direction that there are
22 already other things, cognitive behavioral therapy

1 or whatever.

2 DR. MICHNA: Right. Again, pain is - there

3 area many different types of pain: visceral pain,

4 neuropathic pain. So to this discussion, there are

5 so many sub-discussions that would go on. I don't

6 think we have the time for it right now to go

7 through everything.

8 But certainly, for an acute injury pain or

9 acute postoperative pain, certainly, opioids play a

10 significant role in that therapy. And again, it

11 depends on the patient, and you have to know that

12 patient and what risk factors according to that

13 patient. And maybe your treatment plan would

14 change based on that knowledge. So somebody that

15 is a very high risk of misuse and abuse who has

16 shown propensity in the past, in that situation,

17 depending on the type of pain, opioids would maybe

18 not be high on the list, whereas somebody else,

19 they would be much higher than the alternative that

20 you would use for that patient.

21 It's hard for me to explain in general, but

22 that's why you have to individualize care. And we

1 have to take a more sophisticated approach to pain
2 treatment.
3 MS. CHAMBERS: Thank you. So I don't think
4 we have many statistics to help us. Thank you.
5 DR. STAFFA: This is Judy Staffa. I can
6 offer some information on that from this morning.
7 I know we were asked about new versus refill
8 prescriptions as a crude marker. Dr. Gill went
9 back and looked. Between 2007 and 2011, the period
10 she examined, it's pretty consistent that for
11 hydrocodone combination prescriptions, about
12 80 percent each year are new, and 20 percent are
13 refill, remembering that that's a very large
14 number.
15 MS. CHAMBERS: Thank you. That helps.
16 DR. STAFFA: So if that's an indication,
17 plus it's kind of aligned with what we saw for the
18 indications and the duration of use, that a lot of
19 this seems to be shorter term. But there is some
20 longer term because 20 percent of 131 million
21 prescriptions is still a pretty hefty number.
22 MS. CHAMBERS: Thank you. That's what I was

1 hoping to hear.
2 DR. J. WOODS: Thank you.
3 Ms. Phillips.
4 MS. PHILLIPS: This is a policy development
5 question for DEA. And we've heard from other
6 discussants about the pool, the reservoir of unused
7 or leftover medications as a source for diversion
8 and a source for abuse. So the question is what's
9 in the future, what's in the planning for FDA to
10 promote programs to get that unused drug out of the
11 market, such as take-back programs and others.
12 MR. RANNAZZISI: Within the last four weeks,
13 five weeks -- within the last four or five weeks,
14 we published a Notice of Proposed Rulemaking for
15 the disposal of -- transfer and disposal of
16 controlled substances. I encourage you to open up
17 that Notice of Proposed Rulemaking, which is on our
18 website and also at regs.gov and look at it.
19 It basically establishes the framework, the
20 infrastructure, for a nationwide collection and
21 disposal system. All of the agencies, HHS with
22 FDA, EPA, ONDCP, DEA and the Department of Justice,

1 in addition to several other agencies and the
2 military, work very hard to try and make this work.
3 Is it perfect? Probably not. But if you
4 look at the Notice of Proposed Rulemaking, you'll
5 see a very good beginning for an infrastructure,
6 and we welcome your comments. We want your
7 comments because the rulemaking process doesn't
8 work unless the public comments, or the
9 professional organizations, or the professionals
10 that are affected. If you don't comment, we're
11 only going by what we know and not what you know.
12 So please, I welcome your comment. But
13 there will be within the next -- once the Notice of
14 Proposed Rulemaking is -- we complete the comment
15 period, we're going to immediately go to final
16 rule. We look at all those comments. We comment
17 on them. We take them into consideration, make the
18 corrections we need, and then go to final rule.
19 But we intend to do that quickly because we need to
20 get the drugs out of the houses.
21 In the meantime, we do have a national
22 take-back program. Is it in April, John? April.

1 Again, it's a multiagency, federal agency
2 and state and local agency initiative. You'll have
3 state and local police officers out there with the
4 regulatory boards. I know FDA and HHS is a big
5 part of this, as is ONDCP and the other federal
6 agencies. And this will be the last one if we can
7 get this final rule done. If this final rule gets
8 done, we will never have to do a national take-back
9 program again.
10 DR. J. WOODS: Thank you. Dr. Hopkins.
11 DR. HOPKINS: Thank you. I think this is a
12 general question maybe for FDA people, maybe for
13 Dr. Michna. But is there any information about the
14 number of individuals who have become addicted to
15 these medications who started out using the
16 medications for legitimate pain purposes but became
17 addicted, as opposed to the numbers who are using
18 chronically because they are generally substance
19 abusers in their lives? Any information at all or
20 any thoughts about what that proportion might be
21 because I know there are many people who start
22 using the medications for legitimate pain and

1 become addicted and then become habitual users.
2 DR. KLEIN: There will be a couple more
3 discussions later on this afternoon by the American
4 Association of Pain Medicine and other groups as
5 well that can address that point.
6 DR. J. WOODS: Thank you, Michael.
7 DR. MICHNA: I think the data's pretty poor
8 on that. I don't think we really know the answer.
9 I wish we did. That would help us. Again, we need
10 a lot of research in this area, and we need funding
11 for it. I mean, that's part of what we have to do.
12 And if we don't that, these bits and pieces are not
13 going to solve the problem.
14 DR. J. WOODS: Dr. Cooper.
15 DR. COOPER: This is a question for
16 Dr. Sharon Walsh from this morning. I'll start as
17 you walk. I think one of the things in
18 Dr. Nelson's recent question really highlighted,
19 one of the difficulties or the things we're going
20 to have to wrestle with in our discussion tomorrow
21 is what does it mean when it talks about high
22 potential for abuse in the language? Is that for

1 abuse related to medical use, as the last question
2 asked, or is that related to abuse or recreational
3 use or misuse?
4 My question for you relates, Dr. Walsh, to
5 your slides 9 through 11, where you showed the
6 likability, coasting, those kind of things,
7 comparing the higher doses for hydrocodone
8 combinations compared to morphine and oxycodone.
9 And the question relates to the issue of dose.
10 So if at the higher doses, would we be able
11 to summarize or to conclude from your data that at
12 higher doses, the hydrocodone combinations are very
13 similar to morphine and oxycodone?
14 DR. WALSH: Yes, is the simple answer.
15 DR. COOPER: I tried to make is yes/no.
16 Yes. Then my second question is, would you agree,
17 based on the data from your group using the
18 Appalachia cohort of persons who abuse drugs, that
19 the recreational use or the misuse of these drugs
20 is at much higher doses than recommended? I know
21 our DEA speaker gave us anecdotal evidence of 80
22 pills a day. What sort of range of dosing are you

1 seeing in that cohort of individuals?
2 DR. WALSH: With opiates, with drugs other
3 than heroin, when we see people who are coming in
4 either because they're seeking treatment for opiate
5 dependence, which means they've escalated to the
6 point of physical dependence, or they're coming in
7 for studies like this, where we're looking for
8 regular sporadic abusers, they're always using
9 super-therapeutic doses. Their dosing is never in
10 the therapeutic range.
11 So we see people coming in who are using
12 200, 300 milligrams of oxycodone, for instance, a
13 day, who are dependent. We see people using very
14 high doses of tramadol as another example. So
15 unless there is a tremendous crackdown and the
16 availability is so low, I don't have people coming
17 in and telling me ever that they're taking a
18 5-milligram tablet of hydrocodone.
19 DR. COOPER: Thank you.
20 DR. J. WOODS: Dr. Perrone.
21 DR. PERRONE: I had a question for
22 Dr. Dormitzer about slide number 31. I think we

1 are worried about the initiation -- I think the
2 hydrocodone as Schedule III and oxycodone as
3 Schedule II is sort of a surrogate for doctors want
4 something that's not so significantly concerning as
5 a drug. And just because it's Schedule III, that's
6 perhaps how we're using it, whether or not the data
7 we're seeing here today shows that they're
8 equivalently concerning.
9 But I was wondering on this slide why it
10 seemed in three out of four of these years,
11 hydrocodone was the cause of new initiation. But
12 this data is pretty old. And I was wondering if
13 you looked at 2006 through 2010, which is probably
14 available, would that trend continue? As we have
15 115 million prescriptions or 130 million
16 prescriptions by now, are we seeing even more of
17 hydrocodone as the new initiate, or do we not have
18 that analysis?
19 DR. DORMITZER: At the time, we used these
20 years because these were the data that were
21 provided to us by DEA. And the reason why I used
22 initiates was because the way the questions are

1 worded is have you ever used a pain reliever in
2 your lifetime? If the person responds yes, then
3 they're given a pill show card and said, okay,
4 which one? Then they go on to ask questions or
5 query about last year use. Have you used a pain
6 reliever in the past year? But again, it's pain
7 relievers. So what is not clear is among past year
8 use, how many were for each of the -- I
9 can't -- there's no way to differentiate between
10 the substances.
11 With initiates, they did say I used
12 these -- non-medically used these drugs. But then
13 they give the year or they say how old they were.
14 They say how old they are, and then they say how
15 old they were the first time they used the drug.
16 So now we know that it is that they initiated
17 within the past year. And so now we can
18 distinguish between hydrocodone and oxycodone.
19 So that's why we were using this measure,
20 only because it was the only way to differentiate
21 between the substances in the pain reliever class.
22 Does that make sense?

1 DR. PERRONE: So are you saying if you go
2 forward in the data, you don't have that ability to
3 separate or just --
4 DR. DORMITZER: No, no. It actually has
5 been pretty equivocal among the years, and now
6 actually, we could get the data through 2010. But
7 the last time I looked, I actually think I only got
8 it to 2008. So I don't want to -- it's possible
9 that the years I didn't look at, the things
10 changed.
11 But generally, it's been, like I said,
12 equivocal. It's very wobbly. It seems one year
13 it's hydrocodone, the other year it's oxycodone.
14 And so it has been going up and down like this. So
15 they don't -- but these are initiating -- in other
16 words, you've taken for the first time these drugs
17 just for the experience that it caused, not
18 prescribed to you and for the experience that it
19 caused. So these are --
20 DR. PERRONE: I mean, at least even if
21 they're equivalent, it still acts like the same
22 kind of gateway drug that oxycodone is, whether

1 it's Schedule II or III. Right?
2 DR. DORMITZER: Well, the gateway part, I'm
3 not sure about because I don't know about their
4 other drug behaviors.
5 DR. PERRONE: But if this is their
6 initiation, this is their first experience, this is
7 what we're doing to these people --
8 DR. DORMITZER: This is their first
9 experience with pain relievers, so they could be --
10 DR. PERRONE: But these are people entering
11 treatment programs.
12 DR. DORMITZER: No. This is the National
13 Survey on Drug Use and Health. These are people
14 who are answering the survey. So they may not be
15 dependent. They may not have medical events.
16 These are just --
17 DR. PERRONE: But they're admitting non-
18 medical use.
19 DR. DORMITZER: -- self-report of I took
20 these drugs to get high, basically.
21 DR. PERRONE: Okay. So I guess it's out
22 there. So I mean, I guess my concern is that

1 doctors want a Schedule III drug, but I'm not sure
2 that this is the right Schedule III drug. We want
3 something that's less -- in order to satisfy our
4 patient expectations and to treat pain, but we
5 don't really have a drug that's different from our
6 Schedule II drugs, even though we're using it as a
7 lesser drug. It's not seemingly a lesser drug from
8 the data we're seeing here.
9 My second point is about education, which is
10 for all of the prescriptions that we're
11 prescribing -- and I work in the emergency
12 department, and I see a lot of substance problems.
13 And I've seen it evolve over my years of practice.
14 But for one of the education initiatives, I saw
15 that NIDA and MedPage came out. There was actually
16 an example of a young girl who came to a doctor's
17 office and was getting a prescription for -- I'm
18 not even sure if it was hydrocodone or
19 oxycodone -- for an ankle sprain. And then she
20 came back every two weeks to get it refilled.
21 I don't know what kind of lesson we're
22 teaching doctors if that's the example of how we

1 should be prescribing, when in my heart -- and I
2 see a lot of ankle sprains, I don't think I'm
3 teaching my residents and fellows to prescribe
4 opioids for ankle sprains. And so musculoskeletal
5 is another big indication, and yet we have this
6 whole problem with what are we prescribing for to
7 begin with.
8 Let's look at what Dr. Nelson said about
9 acute pain and sort of outlining what doctors
10 should and shouldn't be thinking about in terms of
11 what is appropriate prescribing. We have 116
12 million patients with chronic pain, but why do we
13 have that? Thank you.
14 DR. J. WOODS: Thank you.
15 We can now take a break, a 10-minute break,
16 and we'll come back then. That would be about
17 3:50. Don't talk about anything other than your
18 favorite dog.
19 (Whereupon, a recess was taken.)
20 DR. J. WOODS: We'll now proceed with
21 presentations from the professional organizations.
22 The first presentation will be by the American

1 Academy of Pain Medicine delivered by Dr. Webster.

2 **Presentation - Lynn Webster**

3 DR. WEBSTER: Hello, everyone. Good
4 afternoon. I'm a little hoarse, a little cold, so
5 I have to drink a little water every little bit. I
6 apologize for slowing the process down a little
7 bit. But thank you for the invitation. Thank you
8 for the opportunity. The American Academy of Pain
9 Medicine appreciates this opportunity to speak to
10 you today.

11 The way we see this is that this is really a
12 balancing act. It's a real challenge. I think
13 this is a tremendously difficult issue for the FDA,
14 I think for our country to address. This is
15 essentially a tradeoff between access for people
16 who derive benefit from hydrocodone and the non-
17 medical use that has caused a great deal of harm.
18 And no one can dispute that there's been a great
19 deal of harm from all prescription drugs, including
20 hydrocodone.

21 So the questions we asked, that you asked
22 yourself is, will the rescheduling of hydrocodone

1 reduce diversion? Will it reduce abuse and
2 addiction? Will opioid deaths be decreased? Will
3 it reduce the access to hydrocodone for pain? Will
4 there be a balloon effect? Will there be
5 unintended consequences that are worse than if not
6 rescheduled?
7 We all know this, that there are really two
8 major groups for whom the hydrocodone formulations
9 and compounds are used, the acute pain and the
10 chronic pain. The volumes are unclear about how
11 much, at least in my mind in the data I've
12 reviewed, as to how much is used for both groups.
13 We know this, too. It's been reported
14 earlier about the amount of drug that has been
15 diverted for non-medical use. A large percent
16 really comes from people who have received a
17 prescription for a legitimate medical purpose. The
18 question is, this is true -- or the statement is
19 that this is true for all opioids, whether they are
20 Schedule II or III.
21 So the wide availability of opioids are,
22 really in the non-medical use, part of the leftover

1 medications, as we know. In one study out of Utah,
2 the University of Utah, post-op patients from the
3 urology department, two-thirds of the opioid
4 prescribed is hydrocodone. Two-thirds of those
5 opioids several weeks later were never used and
6 never intended to be used. There were never any
7 instructions on how to dispose of those
8 medications, and almost all of the individuals
9 chose to keep their medications at home.
10 If hydrocodone was rescheduled, would it
11 change this data? We've seen this data in many
12 different forms as well. Hydrocodone is a
13 significant reason or it's mentioned in numerous
14 times for emergency room visits, but less so than
15 oxycodone, which is a Schedule II.
16 Yet as we've seen an increase in the amount
17 of hydrocodone prescribed nationally, we've seen an
18 increase of hydrocodone associated with toxicities
19 and emergency room visits. There is a parallel
20 association.
21 Deaths in three states reported here,
22 looking at the death rate per 100 kilograms

1 morphine equivalent. And, yes, there's a lot of
2 dispute about what that really means, but it's a
3 way to try to quantitate and then compare.
4 Hydrocodone death rate is 14.3. Oxycodone is 8.7
5 when you're looking at multiple drugs. But
6 methadone is 33.6, and that's a Schedule II. When
7 you're looking at only a single drug associated
8 with the deaths, hydrocodone and oxycodone are
9 comparable but far less than methadone at 9.7.
10 So it's our contention, and I believe I've
11 heard today others say, that hydrocodone is
12 similar, but we believe not the same profile in
13 its abuse potential as the Schedule II opioids
14 biologically, physiologically and
15 pharmacologically.
16 This data has been previously shown to you.
17 I placed the red bars so that I could show and
18 illustrate that there is a difference,
19 statistically possibly but not necessarily
20 clinically, and we don't know really what
21 difference between the mean liking or the mean high
22 of one opioid to another ever relates to a clinical

1 setting. We don't know that.
2 The various means of oxycodone, morphine and
3 hydrocodone, again from the same study of Stoops,
4 looking at the higher dose, which is not available
5 at 20 milligrams of hydrocodone, is comparable to
6 morphine, yet oxycodone is slightly higher. So
7 very similar, very similar to Schedule IIs with the
8 data.
9 We always look in human abuse liability
10 studies at two primary endpoints. That is, the
11 degree to which a drug is reportedly causing them
12 to feel high, the euphoric effect, or their liking
13 effect.
14 Here looking at the difference between
15 morphine and hydrocodone, you see a difference of
16 10 at the 10 milligram dose for high and 11.9,
17 essentially 10 in both instances. One paper exists
18 in the literature that suggests a 10-millimeter
19 difference is clinically significant. I'm not sure
20 that we can say that one paper is something we can
21 rely on.
22 When you compare oxycodone to hydrocodone,

1 the differences are more, 15 to basically 17. So
2 they're similar but not the same in the tools that
3 we use to assess the abuse potential of opioids.
4 Potential consequences of scheduling change,
5 probably less drug will be prescribed. I think
6 that's probably certain. More frequent visits and
7 more co-pays. Higher insurance costs for Medicare
8 and Medicaid and commercial payers because of more
9 frequent visits and more prescriptions. Patients'
10 access to the medication and treatment may be more
11 difficult.
12 There are benefits, of course, too. Greater
13 care in prescribing. Schedule IIs require more
14 monitoring. Patients have to be seen more often.
15 And if there's less prescribed, there's less
16 available for the illicit non-medical use; and
17 fewer people likely to be exposed to have the
18 vulnerability to the disease of addiction and
19 probably fewer overdose deaths.
20 Potential risks, though, of scheduling
21 change; there is a serious concern about access for
22 the people who have a legitimate pain problem; may

1 have less effective medications prescribed because
2 of the hassle of Schedule II prescribing; more
3 dangerous substitutions could be prescribed. If
4 they choose to stay within opioid, for example,
5 methadone, we know that that is associated with
6 much greater risk than hydrocodone. Failure to
7 treat pain is a risk. Increased cost, as I've
8 already mentioned.
9 So the alternatives also bring risk.
10 There's a balloon effect. The side effects and the
11 risk to using drugs that would not be a Schedule II
12 if hydrocodone were placed as a Schedule II,
13 codeine, seizures, not effective; tramadol,
14 seizures, serotonin syndrome; NSAIDs, heart
15 disease, liver disease, kidney disease.
16 Benzodiazepines, we find that some physicians will
17 use benzos instead of opioids, and it has its own
18 inherent abuse and addiction and overdose risk; and
19 a possible risk in illegal drug use. As we've seen
20 OxyContin abuse deterrent formulations replace the
21 old OxyContin, some patients have gone to use
22 heroin.

1 The bottom line is if we're addressing a
2 substance abuse problem in the country and with
3 individuals, we need to take into consideration
4 that it's not just the drug. It's the environment
5 and the genetics of an individual that contribute
6 to the abuse and the disease of addiction.
7 Certainly, availability, abundance of drug in our
8 communities will contribute and has caused some of
9 the problem.
10 Regardless of whether there is rescheduling,
11 there are some key things that need to be taken
12 into account and probably considered. We need
13 better education. That's been well addressed. We
14 need to address the knowledge gaps in acute,
15 subacute and chronic pain. We need to begin
16 educating in medical schools and throughout our
17 practices. We need to manage with safety in mind
18 and initiate comprehensive multidisciplinary care
19 for the chronic pain patient.
20 There is no risk-free solution. Changing to
21 Schedule II has risks. Leaving the drug at
22 Schedule III has risks. Failing to educate either

1 way is a risk. Failing to treat pain will leave
2 some suffering. And failing to stop the incautious
3 prescribing we've observed over the last two
4 decades is a risk.
5 So changing from Schedule III to II will
6 change a treatment paradigm, the historical ways in
7 which we've been treating acute and subacute pain.
8 May not be able to anticipate the far-ranging
9 impact upon our healthcare system. Access will
10 likely decrease. There will be a likely balloon
11 effect.
12 Reducing opioid harm must focus on biology
13 and the social risk factors, not only the drug.
14 Financial impact is undetermined. Impact on the
15 non-medical use versus the untreated pain is
16 uncertain. Regardless of what happens, we need
17 better data. We need research. And if there is a
18 rescheduling, we certainly need to measure and
19 assess the impact that it has on the harm on people
20 who should not be receiving it as well as the
21 people who deserve access. Physician and patient
22 education must improve regardless of the schedule

1 classification.

2 Thank you. Questions later, right?

3 DR. J. WOODS: Our next speaker is

4 Mr. Simenson from the American Pharmacists

5 Association. Simenson he will probably say should

6 he be pronouncing it correctly.

7 **Presentation - Marcie Bough**

8 DR. BOUGH: Good afternoon, everyone. I'm

9 Marcie Bough with the American Pharmacists

10 Association. I'm accompanying with our incoming

11 president, Steve Simenson, a frontline pharmacist

12 and pharmacy owner from Minnesota. We very much

13 appreciate the opportunity to be here today and

14 provide some overview for the potential impact on

15 pharmacists.

16 A little about APhA, we represent

17 pharmacists in all different practice settings. We

18 have about 62,000 members that are pharmacists,

19 student pharmacists, scientists and pharmacy

20 technicians. And, again, they practice in all

21 different settings.

22 The goal of our presentation is really to

1 fulfill the request of FDA and provide the
2 committee with an overview of the potential impacts
3 and things to consider for what rescheduling would
4 do for the pharmacy process and what pharmacists
5 would deal -- that could ultimately impact patient
6 access and really highlight the difference of the
7 life of a C-II prescription versus the life of a
8 C-III prescription through a pharmacy.
9 We really do appreciate the information we
10 received from a variety of stakeholders and
11 pharmacy groups. I want to recognize some feedback
12 we received from our leadership and members at APhA
13 and pharmacists from across the country and our
14 colleague pharmacy organizations. NACDS, NCPA and
15 ASCP provided me with some great information.
16 We also got some good feedback from the
17 Uniform Services and the federal pharmacy
18 community, and then, of course, referenced DEA
19 information, and ultimately did our own internal
20 analysis of the 50 states back in October for the
21 first scheduling of this meeting, where we tried to
22 look at some of the nuances with state laws and

1 regs that we'll highlight in a few slides. Some
2 mirror what's in the Controlled Substances Act, but
3 there's a few differences.
4 So here's an overview of pharmacy issues to
5 consider. We certainly support from the pharmacy
6 community patient access to pain medications for
7 legitimate medical purpose, but with that balanced
8 approach that we've heard throughout the day to
9 help address prescription drug abuse, misuse and
10 diversion, but ultimately ensure appropriate pain
11 management. And we very much support the
12 regulatory process in which this discussion is
13 moving forward with this meeting here today
14 considering the rescheduling.
15 There's going to be a lot of questions that
16 remain about the positives and negatives that we've
17 discussed today on the impact of rescheduling, but
18 we do know that they'll be different impacts on
19 different practice settings for pharmacy, just like
20 medicine or different areas within the supply
21 chain. There's going to be different impacts
22 across the practice settings.

1 There's also an impact on supply chain
2 logistics. We'll go through some visuals and then
3 backup text on that that Steve will go through, and
4 then ultimately some of those differences with the
5 states.
6 So we're going to look at some of the
7 specific pharmacy issues that we want you guys to
8 consider as you're making your final
9 recommendations tomorrow to FDA. And just from an
10 impact perspective for pharmacy, we've heard
11 throughout the day the significant number of
12 hydrocodone-containing product prescriptions moving
13 through the healthcare system each year. We've
14 heard reference to twofold, threefold increase
15 amount of hydrocodone products moving through.
16 There is at least 20 different products and
17 thousands of different combinations in which
18 pharmacists are interacting with the products we're
19 dispensing. And as we've heard, there's over a
20 million -- millions of different prescription
21 orders being dispensed through pharmacies
22 throughout each year.

1 In some pharmacies, as was discussed earlier
2 this morning with refills, we did get some
3 information that in some pharmacies, there could be
4 nearly 40 percent of new hydrocodone prescriptions
5 that have a refill. Some may be more or less. It
6 depends on that patient population and the
7 community in which the pharmacy is located. But
8 there is a challenge with how a refill is dispensed
9 versus a new prescription, mostly from a timing,
10 workflow and logistics perspective.
11 There's a significant difference in the
12 number of prescriptions per week in a pharmacy,
13 again depending on the patient population and
14 location, and it may range from a few C-IIs a week
15 to 50 to hundreds. And it just depends on the
16 location, and that changes the impact which
17 ultimately changes patient access considerations as
18 you consider all of the information you're
19 receiving throughout this meeting.
20 We do know that any sort of a reschedule or
21 that consideration would have an impact on the
22 entire pharmacy supply chain. This visual

1 indicates the variety of different areas in which
2 we access our products. So when you look at -- the
3 patient is at the end, and ultimately, that's where
4 we're trying to get the medications. But for the
5 pharmacy to receive the medication, first it has to
6 have the raw materials, go to a finishing product,
7 go through the manufacturers, packaging, wholesale
8 distributors, and then ultimately to the pharmacy.
9 I'm going to turn the presentation over to
10 Steve to highlight some of the differences in that
11 life of a C-II versus life of a C-III prescription,
12 moving through the pharmacy component of our supply
13 chain because that's why there's a potential impact
14 to consider for patient access moving forward.
15 **Presentation - Steve Simenson**
16 MR. SIMENSON: Thanks, Marcie. I appreciate
17 that very much.
18 It's difficult for a provider or prescriber
19 to make the right decision to provide a scheduled
20 drug to a patient. But it's also difficult in a
21 lot of cases to get that medication to the patient
22 in the correct dose, the right directions and the

1 right instructions to take it like it's supposed to
2 be taken.
3 In a normal process, we've got the
4 wholesaler on one side where the pharmacy orders
5 the prescription. Class III prescriptions and IV
6 and V can be ordered just like any other
7 prescription along with your regular prescription
8 order. They're added to your inventory daily.
9 There's a requirement to inventory them in the
10 pharmacy at a point in time every two years and
11 make sure to adjust to what you're using.
12 Inventory is stored alphabetically. It's
13 easily accessible and managed by your staff. And
14 as pharmacists and what they do in dealing with
15 patients and providing care to patients are
16 delegating more and more of the responsibilities in
17 most pharmacies across the country. By doing that,
18 they're having technicians and other auxiliary
19 staff doing the ordering, putting an order away,
20 and helping us enter prescriptions.
21 On a Class III, IV or V prescription, a
22 prescription can be written and given up to five

1 refills and filled over a period of up to six
2 months. We can transfer it over the phone to
3 another pharmacy with prior documentation and make
4 it easier for a patient to get it at another
5 pharmacy.
6 With a Class II prescription, a lot more of
7 paperwork and administration is added to that. We
8 can only order Class II prescriptions by a process
9 that requires a special form from the DEA. We can
10 do it online now, and it's called CSOS program.
11 But only a pharmacist can sign that form. Only a
12 pharmacist can order Class IIs. The pharmacist in
13 charge is in charge of ensuring that all the
14 Class IIs are taken care of, stored appropriately,
15 and dispensed appropriately.
16 The verification of prescription stays the
17 same with the pharmacists, but there are a lot of
18 extra steps and rules along the way that are
19 required in order to get that prescription in the
20 store and get the pharmacist to have the right
21 inventory to provide to their patients.
22 There are no refills on those prescriptions.

1 We can't transfer them to another pharmacy. We
2 can't partial fill those prescriptions. We have no
3 emergency filling other than in certain long-term
4 care facilities on prescriptions. So there's a lot
5 more rules and regulations to govern how those
6 prescriptions are handled.
7 If hydrocodone is rescheduled to Class II,
8 the orange boxes give a lot of -- there's several
9 bottlenecks in the system, extra administrative
10 steps with the DEA forms, extra steps in the
11 process with the wholesaler. The order is
12 separated and sent separately. You cannot call in
13 an order. They have to have the form or the CSOS
14 paperwork electronically sent to them.
15 There's more need for prescriber visits,
16 being they need an initial prescription to get
17 their prescription filled. If it's an emergency,
18 it's at night, after hours, a prescriber cannot
19 call in that prescription.
20 What we have seen -- and I know there's a
21 rule that the DEA does allow prescriptions to be
22 postdated, but in my experience, over many years,

1 physicians and other prescribers don't take
2 advantage of that. And on talking to them, I think
3 they have some legitimate concerns about the
4 monitoring and the potential hazards of some of
5 these medications, and don't want to give that up
6 by postdating opiate prescriptions. We see a lot
7 of it in ADHD meds and other type Class II
8 prescriptions, but not in pain control medications.
9 There's a lot more -- we have a continuous
10 inventory. Those medications are monitored daily,
11 counted and accounted for on a daily basis. So
12 there's very little, if not any, potential for
13 diversion out of that pharmacy side.
14 Some of the pharmacy issues to
15 consider -- and on these slides, we'll get a little
16 down into the granular level compared to the
17 visuals earlier, with the Class II forms, the real-
18 time perpetual Class II inventory.
19 Storage and security. Many states require
20 them to be stored in safes. My experience is
21 different than the presentation earlier, that about
22 maybe 50 percent are stored in the inventory,

1 spread out through the inventory. Fifty percent
2 are required by states or company policy to be
3 stored in safe-type facilities in the pharmacy,
4 which adds to the time, the recordkeeping until you
5 get them out and dispensed them to patients.
6 Due to the sheer volume of hydrocodone
7 products out there -- and there are a lot of
8 prescriptions, as you've seen all through the day,
9 on hydrocodone -- these extra requirements, extra
10 storage, extra monitoring, would take a lot of time
11 for the pharmacist, which takes them away from
12 doing their clinical work with patients.
13 The workload and workflow would have to
14 change. There have to be a time to implement.
15 You'd have to have new policies and procedures,
16 potentially hire more staff, more pharmacists to do
17 some of the work the pharmacist does on other
18 things. Some chains have estimated those costs in
19 the millions of dollars when you're rolling them
20 out to 8,000, 10,000 stores.
21 Lots of administrative costs. This policy
22 has to be done correctly every time. There's no

1 room for error, and pharmacists do that very well
2 and are willing to do whatever it takes to keep the
3 drug chain safe. But there are a lot of extra
4 steps and a lot of work that it takes.
5 There's a lot of impact on the patient care
6 process and access. Having talked to many health
7 providers over the years and recently knowing I was
8 going to testify, nurse practitioners, physician's
9 assistants where they can prescribe Class IIs and
10 physicians, there's a group of those practitioners
11 who decide not to use Class II drugs. They've
12 decided they don't want it to be part of their
13 practice, and it's an unnecessary hassle.
14 In Minnesota, the state board has not
15 approved Class II ordering electronically. They've
16 approved Class II ordering but haven't approved
17 faxing Class IIs. Most of our prescriptions,
18 95 percent in Minnesota, come over an e-prescribing
19 system, and we still have to order and take
20 Class II prescriptions separately. We have to have
21 a physical copy in our hands before we fill those
22 prescriptions.

1 Access, I think is one of the biggest things
2 I'm concerned about as a pharmacist. We have a lot
3 of older patients that are homebound; getting an
4 emergency prescription or a prescription for a
5 group home and what it takes to get that
6 prescription being we need a written copy. Every
7 month have to get a new prescription from the
8 physician. And like I said earlier, most
9 physicians in our market like to have that new
10 prescription and send it to us. It takes us about
11 72 hours to get a new prescription.
12 Part of the process of filling that I
13 mentioned earlier, in Class IIs, a lot of seekers,
14 as we call the patients that are looking for
15 addictive medications, we double count all our
16 Class IIs so there's no question if they say they
17 were shorted or didn't get all the prescriptions
18 that they were entitled to. That adds time in the
19 process but does add to accuracy, and then there's
20 not a question of whether those prescriptions were
21 given out correctly.
22 Marcie, could you continue on long-term

1 care?

2 **Presentation (continued) - Marcie Bough**

3 DR. BOUGH: So there's been a lot of

4 discussion about kind of outpatient pharmacy,

5 knowing that this isn't really applicable to

6 changes that would be on the inpatient perspective,

7 but we did want to highlight some differences with

8 long-term care pharmacy. When you think about

9 Medicare Part D implementation, long-term care is

10 classified as outpatient pharmacy and has to go

11 along with differences in how things work within

12 long-term care settings versus the outpatient

13 settings.

14 So this slide just highlights that there is

15 a pharmacy staff, medical staff contact, regarding

16 the hydrocodone prescriptions that would need to

17 increase from once every six months to that monthly

18 interaction. There's a unique kind of prescribing

19 and dispensing process in long-term care settings

20 where often the pharmacy may be delivering product

21 to the setting and there might not be a physical

22 pharmacy on the site. And there may be utilization

1 of nursing staff to transmit prescription or chart
2 orders for products but not allowed for C-IIs.
3 There's not always a physician on site.
4 They might be rotating around in the hospital,
5 coming on site, but they're not physically on site
6 all the time. So there may be patient delay. When
7 you think of getting in touch with a physician,
8 trying to get a new prescription order for C-IIs,
9 we already experience that in the setting right
10 now. Hydrocodone products would add to that. If
11 it does move that way, processes would be
12 implemented, but it does have an impact on patient
13 care and the appropriate treatment of pain in a
14 manner that assures that the facility isn't subject
15 to potential citations and state inspections from
16 other requirements in those practice settings.
17 Again, it would put restrictions on staff
18 who might be handling C-IIs compared to the other
19 prescription products. And then there may be
20 challenges or different implementation processes
21 for storage in safes or how those might be managed
22 onsite.

1 Earlier I mentioned we did an internal
2 policy analysis of the state laws and regs and D.C.
3 for prescription products, and specifically
4 highlighted looking at controlled substances.
5 We've heard today about the overall requirements
6 for C-IIs coming from the Controlled Substances
7 Act. I won't go through that. But some of the
8 states are either mirroring or supplementing or
9 otherwise addressing C-II activity, and we're going
10 to go through that because it may repeat some of
11 what's in CSA, but it may be more specific.
12 Some folks suggest that the security issue
13 may be the biggest impact with the states that have
14 this difference. This is just a list of states in
15 which we really have specific security requirements
16 for those C-IIs, and it's 14 on this slide.
17 When we look at dispensing or dispersing
18 products throughout the inventory, we heard earlier
19 today that this happens a lot. It might be
20 authorized to dispense throughout the entire
21 inventory within a pharmacy, but generally, we hear
22 from pharmacies and owners that they generally use

1 safes and are not dispensing throughout the
2 inventory.
3 There are additional requirements that may
4 be slightly different from CSA when it comes to
5 perpetual inventory, so that may be an additional
6 requirement on the states where there's additional
7 requirements. And when you look at documentation,
8 filing, paperwork, recordkeeping, there's some
9 states here listed that have separate prescription
10 file requirements for the pharmacies on C-IIs. And
11 there's also some specific provisions related to
12 inventory and recordkeeping requirements for C-IIs.
13 There's also some states with specific
14 labeling requirements in which there might be
15 certain text that might need to be printed out on
16 the label that's different from what's in CSA. And
17 there's also some additional requirements upon
18 dispensing that may relate to documentation on the
19 original prescription order itself as to whose
20 dispensing date and appropriate documentation for
21 those state requirements.
22 So this slide, I think it's 35 or so,

1 generally reflects not being able to refill a C-II,
2 but they put it in the state laws as well. And
3 then there's a few nuances within state
4 requirements that aren't really addressed in the
5 Controlled Substances Act. There's two states
6 where there would be an impact on what pharmacists
7 have the authority to practice through
8 collaborative practice agreements with medical
9 community. There are two states where there's a
10 requirement for pharmacists to check the patient's
11 ID for dispensing a C-II. And then there's also
12 some laws for two states requiring additional
13 requirements for out-of-state pharmacies.
14 So now we're going to focus on other
15 activities and close out our presentation with
16 looking at what's working well, those provisions
17 that pharmacists are engaged in that we want to
18 support and continue to see the implementation to
19 ensure patient access while we'll continue to help
20 address the overall effort on addressing
21 prescription drug abuse, misuse and diversion.
22 When we look at these overall activities to

1 first balance that patient access and patient care
2 and patient safety, we do look on why these burdens
3 and impacts on pharmacists and pharmacies have an
4 impact on that access. And ultimately, like we've
5 heard earlier today, we need a balanced approach so
6 that we're having an effective process moving
7 forward and not just making work for the sake of
8 work.
9 We want to ensure that we're limiting burden
10 but that any activity moving forward considers
11 those impacts for medicine, pharmacy, wholesalers,
12 manufacturers, the whole pharmacy supply chain as
13 we move to ensure patients have access to
14 appropriate pain management.
15 We also want to focus on what's working well
16 and what we can learn from those programs to
17 implement across the board. We very much support
18 the ongoing efforts of the White Office of National
19 Drug Control Policy and the National Drug Control
20 Strategy, and then with what the HHS agencies are
21 doing that.
22 So when we look at some of those key focus

1 areas on education, we've heard earlier today on
2 some of that activity, but I just want to reiterate
3 that there is increased focus and awareness on
4 opioid safe use in pain management and, ultimately,
5 safe medication use and the education that goes
6 with that. And the panel earlier, there was good
7 discussion on education front and how we can help
8 with appropriate prescribing practices, dispensing
9 practices and ultimately helping the patient engage
10 in their own medication management.
11 When we look at FDA's risk evaluation and
12 mitigation strategies, or REMS programs, the opioid
13 dialogue really helped drive increased awareness of
14 the challenges and the problems we're facing with
15 prescription drug abuse, but it has equally
16 challenged the healthcare community to find ways to
17 get the education to the prescribers, engage the
18 pharmacists in the process, and then ultimately
19 engage the patient in the management of their
20 medications again.
21 We also like that the ONDCP has its own
22 training tool that can help facilitate ongoing

1 education just like I think probably most of the
2 healthcare provider communities have ongoing,
3 continuing education and awareness information.
4 Pharmacists and APhA and the other pharmacy
5 organizations have that as well, where we really do
6 try to focus education and outreach and engagement
7 from pharmacists on appropriate pain management and
8 engagement with the patient, but also awareness of
9 the opioid management and prescription drug abuse
10 issues.
11 There's also a lot of partnerships with
12 community outreach and education programs. There's
13 a lot of great examples of what the schools of
14 pharmacy are doing in association with community
15 outreach programs.
16 When we look at disposal and enforcement and
17 e-prescribing activities, we very much see value in
18 pursuing additional and improved options for
19 patients to dispose of their medications. We'll
20 continue to evaluate the DEA Notice of Proposed
21 Rulemaking that was described a little bit earlier
22 because it's a great opportunity to ease the burden

1 on how we can dispose of medications. And we very
2 much support pharmacists' engagement in the
3 national prescription drug take-back programs.
4 Even if we're not collecting sites for that, we are
5 working with pharmacies to get the information out
6 to their communities. And often, there's specific
7 pharmacy, local, community or state programs that
8 pharmacists are engaged in to help facilitate those
9 disposal programs.
10 There's also activity with FDA on how some
11 of the potential abuse and diversion products are
12 being accessed online. The BeSafeRx program and
13 the Safe Use initiative also address these
14 non-regulatory routes to help get information out.
15 We support enforcement of the rogue pain
16 clinics and doctor shoppers and the rogue activity
17 that's out there, whether it's through medicine,
18 pharmacy, or other avenues. We want to help secure
19 and keep secure our supply chain as we continue to
20 address the diversion issue.
21 With regard to e-prescribing, it was
22 discussed earlier. We do support utilization and

1 expansion of e-prescribing of controlled
2 substances. And I have one data set to update you
3 with, that with regard to authority to e-prescribe
4 controlled substances for C-IIs specifically, there
5 are 13 states that currently do not allow that for
6 C-IIs. The others generally allow moving forward,
7 but those 13 states are trying to address those
8 issues and the nuance of how HIT has evolved in
9 advance of what the regs are in place. So
10 hopefully that data is helpful for you.
11 I'm going to turn it back to Steve to
12 highlight some of his innovative practice setting
13 activities and his great work with PDMPs and with
14 medicine in his community to highlight pharmacists'
15 engagement with patients and with doctors on pain
16 management, and then we'll close out. Thanks.
17 **Presentation (continued) - Steve Simenson**
18 MR. SIMENSON: Thanks, Marcie.
19 We have a very robust PDMP in Minnesota. We
20 do use it daily in our practices. A little
21 history. Our practice, we have seven pharmacies,
22 supermarket, traditional, in-clinic pharmacies, and

1 all those sites. The doctors and other providers
2 are calling us on a fairly regular basis to do
3 research during an appointment, where they want it
4 fast or before an appointment, which lets us fit it
5 into the workflow of an evaluation on patients and
6 what their scheduled drug usage, mostly Class II
7 drugs, and also hydrocodone when they need that
8 information. That's very valuable.
9 Because we have pharmacies in the clinics,
10 because we've made relationships with physicians,
11 PAs, nurse practitioners in our community, we've
12 been able to do more things over the years. I'll
13 start with collaborative practices, simple
14 therapeutic substitutions, and different disease
15 states. Now we have eight different disease state
16 collaborative practices where we help them monitor,
17 manage, and medications for those physicians, and
18 answer an awful lot of questions for them.
19 The latest we've got that we've put in the
20 last year involved opiate usage. And what we've
21 done in agreement with physicians is three to seven
22 days before their visit with a patient, they

1 stepped up to the plate and realized on chronic
2 opiate use, they needed to see the patient in a
3 more involved, hour-long visit at least once a
4 year, along with regular shorter visits seeing that
5 patient.
6 So what they do is they send out the
7 patient's name, any information they have on them.
8 Because we have collaborative practice, we have
9 access to their electronic medical record. We can
10 see what their diagnosis is. We can see what their
11 goals are for the patient. We look at the PDMP and
12 see if there's appropriate usage, are they
13 adherent, are they going to multiple doctors, are
14 they going to multiple pharmacies, and give them an
15 evaluation of what we think, if there's a problem,
16 if everything looks good; is there a med they've
17 been on for a long time and the diagnosis is more
18 minor, would they consider switching to another
19 medication. So the doctor has all that
20 information, or the provider, when they're seen for
21 that visit.
22 Then along with regular labs, urinalysis and

1 an hour-long appointment with the healthcare
2 provider, primary care provider, they make a
3 decision, is the medication still appropriate for
4 the patient? Should I change it? Should I change
5 the dosage?
6 We're available for comment if they have any
7 questions and document the evaluation we give them
8 in their electronic medical record. At the end of
9 the appointment, the primary healthcare provider
10 decides what the ongoing plan is. If in the chance
11 the doctor decides to change meds, they talk to the
12 pharmacist, and we give them suggestions, and they
13 pick another medication. If it requires a taper or
14 if they're deciding to discontinue the medication,
15 we help them do the taper and monitor it for them
16 with communication with the patient.
17 It's been very successful in the last year.
18 It's much easier to -- for the physicians that had
19 a hard time saying no, it's been much easier for
20 them to discontinue meds and change meds. It's
21 been good for us because we can give them a
22 different perspective coming on the medications,

1 and as pharmacists, free up more time working with
2 them. It's been a very positive, positive
3 experience.
4 We can answer questions about proper
5 medication disposal. I applaud the sheriffs'
6 offices and the police departments in our area who
7 have set up 24-hour secure collection facilities
8 for patients to get rid of their meds, all schedule
9 meds and any other med, help getting some of these
10 problem meds off -- out of patients' medicine
11 cabinets. That's one of the messages in education
12 that we have to do.
13 The PDMPs have been very, very positive for
14 us. There could be some improvements. We need
15 more states to share them in border communities.
16 In our state, we don't know who the physician who
17 is prescribing the med when we look at the PDMP,
18 although we guess after a period of time. But we
19 need to be able to work with those physicians and
20 send them direct information because there's no
21 contact for us. We have to go through the state
22 reporting agency. That would be very, very

1 positive.
2 But it is a very good tool in monitoring
3 abusive behavior and inappropriate use of opiates
4 in the patient population. They ask us questions
5 on chronic pain, and they appreciate pharmacists
6 being there to give them input on making sure the
7 patient gets the proper care.
8 I look at dentists. I look at surgery
9 centers. Our patient base, most of our hydrocodone
10 comes from acute short-term needs, prescribe two to
11 three days' worth and then reevaluate. One of the
12 keys is finding a way to not allow large quantities
13 unless there is a unique medical reason for that.
14 Sometimes in our communities, we get piles
15 and piles, bottles and bottles from mail order
16 pharmacy. We see that as a real problem when the
17 PDMs and insurance companies encourage them to get
18 a 90-day supply. There's got to be some leeway and
19 some sensible policies and procedures that there
20 are medications that aren't appropriate in those
21 large quantities for patients.
22 There's a lot of opportunities to monitor

1 and manage pain medications in a more effective
2 manner, and I think pharmacists want to be part of
3 the process and make it a safer place. Thank you.
4 DR. BOUGH: So we appreciate very much the
5 opportunity to present and hope that we've provided
6 the committee with some additional insight from
7 pharmacy perspective on things to consider as
8 you're making recommendations to FDA on
9 rescheduling of hydrocodone.
10 Ultimately, we want to consider number of
11 refills, impact on workflow, workload, storage and
12 ordering activities, time and cost to implement so
13 that there's enough time -- if it does get
14 rescheduled, that there's enough time to actually
15 implement the process. And some of those nuances
16 with the different states, that that may delay an
17 implementation as well.
18 But ultimately, it's about patient access
19 and what can we do to help ensure patients are
20 appropriately managed on their medication, or as
21 discussed earlier, the appropriate patient on the
22 appropriate med. We very much look forward to

1 increased utilization of PDMPs and integration and
2 interoperability of those systems within medical
3 and pharmacy operating systems. And then, as Steve
4 described, the collaborative work between the
5 healthcare providers in ensuring we're taking the
6 focus on patient care and moving that forward in
7 finding the appropriate pain management activities
8 that's a balanced and fair approach as we consider
9 the options for moving forward.
10 So we thank you for your time, and good luck
11 with your discussions.
12 DR. J. WOODS: Thank you for your
13 presentation, and I apologize to Dr. Bough for not
14 saying her name under Simenson.
15 Our next presentation is from the dentists
16 and oral surgeons. It will be delivered by
17 Dr. Curro.
18 **Presentation - Frederick Curro**
19 DR. CURRO: Thank you. I'm speaking on
20 behalf of the American Dental Association and the
21 American Association for Oral Surgery. Just a
22 little bit about my background, I am a dentist, but

1 I actually have a PhD in pain management and
2 clinical pharmacology. And it was the first
3 training grant that John Bonica actually initiated.
4 I won't tell you the year, but it was the first
5 one.
6 So part of my job, I can see from the
7 discussions, is to really explain the dentists'
8 role in all of this. And dentists see a spectrum
9 of pain, mild, moderate and severe. And part of
10 that is that in the tooth, if you've ever had a
11 toothache, there is no room or soft tissue around
12 the tooth for it to expand. So all you feel is
13 excruciating pain. And any time that we do a
14 procedure, it involves bone, and bone and the
15 adhering tissue that contains all the nerves is
16 always insulted.
17 Now, the degree of that bone and the degree
18 of what we do to the tooth really dictates to the
19 level of pain. So most of the pain that we do is
20 postsurgical, but most of the pain is also acute.
21 And the last speaker said that acute pain should
22 not be prescribed more than three days, and that's

1 a good guideline. Anything going on after three
2 days would be considered something else going on.
3 So the range of medications to treat this
4 pain -- and don't forget, the end user, or us, is
5 about diminishing pain. And the questions that
6 have been discussed here are actually terrific. I
7 mean, there's a big difference between chronic pain
8 and acute pain for many, many reasons.
9 So the range of the drugs that we have at
10 our disposal are very limiting, and, clinically,
11 hydrocodone has been proven to be very effective.
12 And so it is the drug of choice for a number of
13 reasons, which I'll go through. Codeine, on the
14 other hand, which is a pro-drug -- and all of the
15 spectrum of analgesic drugs have gone through a
16 series of information changes.
17 At one time, we had Tylenol number 1, 2, 3
18 and 4. Then we started to have a lot of the NSAIDs
19 come on the market, and then there was a slew of
20 NSAIDs. And some would work, some would not, some
21 went back to using codeine. Then the issues with
22 acetaminophen came up and the limit of the maximum

1 daily dose of 4,000 milligrams became an issue, and
2 you could push that relatively quickly with
3 somebody in pain.
4 Then in the chronic pain arena, we never
5 used to use narcotics for neuralgias. Now you can.
6 That changed. That was a question asked by someone
7 on the other side there. So the dynamics of the
8 use of these drugs have actually changed, including
9 the number of people prescribing.
10 So the hydrocodone combination products have
11 improved pain management and reduced really the
12 adverse effects generally for dental patients
13 versus codeine. And codeine also has a genetic
14 issue with it, as that information comes out, about
15 15 percent of the people involved. So it's not the
16 best drug. It's almost going backwards actually in
17 the spectrum of pharmacology that we have evolved
18 with.
19 So NSAIDs, another option and part of the
20 conversation of education, which Dr. Zacharoff was
21 talking about. Education and the subtleties in the
22 use of these drugs has been lost, and that's been

1 lost both in medical and dental schools. You can't
2 place these subtleties always at the clinical site.
3 But these NSAIDs, of course, that was
4 another change. When the NSAIDs came out, there
5 was studies showing equilibration with codeine, so
6 codeine went down. But then the other issues came
7 up with NSAIDs and the GI bleeding. And if one
8 looks at the number of deaths just with aspirin
9 alone, as you all know, that's an issue, a big
10 issue, still an issue.
11 So the opioids have their place in the
12 spectrum in management of pain. So hydrocodone
13 combined with ibuprofen, good alternative to
14 hydrocodeine and acetaminophen, and it has an anti-
15 inflammatory component, which is what we seek. And
16 so HCCs can be very useful for these patients,
17 including orofacial pain.
18 Now, facial pain and head pain is a bit
19 different than pain in an extremity. The patients
20 can't separate the pain directly from their head as
21 opposed to pain in the foot. So it gets a little
22 complicated, a little bit more complicated, when

1 you have facial pain or pain of the head origin.
2 So when you look at the role of these, the
3 common denominator for effective pain management
4 control -- diversion now another issue -- really is
5 education. And we don't educate our students on
6 all of these subtleties. As a matter of fact, for
7 full disclosure, I actually chair the working
8 committee for the Patient Provider Agreement, the
9 FDA's Safe Use Initiative. And I didn't actually
10 know that there was a proposed rule on how to get
11 rid of drugs. I just made a note. And we're
12 actually contemplating doing a study on how do you
13 disseminate this information not only to the
14 profession about also to the consumer.
15 That's been a big problem, but we are
16 actually looking at conducting some studies. And I
17 thought that this would be a good time to make you
18 aware of that. This is a terrific initiative
19 that's been going on for about two years now, and
20 we're close to getting a final PPA, or Patient
21 Provider Agreement, with the intent of having it
22 universally accepted. Now, how mandatory we have

1 that or how we hook it up with REMS or something
2 else, that's still to be decided.
3 But it's not an administrative change by
4 moving Schedule III to II. It's an active change
5 where the provider and the consumer is involved in
6 that decision. And that's how you get the
7 information transferred so that you can get active
8 change, in my opinion at least, not by an
9 administrative.
10 On top of that, we're talking now about
11 patient-centric approach and patient-centricity,
12 and the Patient-Centered Outcomes Research
13 Institute. The patient now is going to be playing
14 a much bigger role in their healthcare. They must
15 be involved with all of this now, and that's
16 probably a great vehicle for them to get involved
17 in the disposal of medications, where many people
18 just don't even think about the disposal. We never
19 discuss it, so everybody's guilty along those
20 lines.
21 So when we look at who are the providers and
22 you look at the number of milligrams per patient of

1 prescribed opioids over 10 years and the volume of
2 prescriptions, it really suggests a volume issue
3 for the amount of prescriptions that are written,
4 right or wrongly, but there are many other people
5 involved in writing prescriptions. And we did a
6 couple of surveys with the FDA, and it turns out
7 that physicians are a small percentage that we get
8 a response from. It's the others that are writing.
9 Now, you can talk about what's the
10 educational knowledge, and I'm talking about base
11 knowledge that you have now in interpreting and
12 using these opioids, not a perfunctory knowledge
13 where you just write a prescription. And that's
14 what I think people like Dr. Zacharoff -- and when
15 we talk about education, that's the fine point of
16 the education that we talk about.
17 So what other considerations, the public
18 health benefits of rescheduling HCCs from C-III to
19 C-II, would they outweigh the risks and costs, and
20 would the proposed schedule change significantly
21 reduce drug diversion?
22 Now, drug abusers and chronic pain patients

1 are very resilient patients if they're out to get
2 their drugs. And I have 20 years in treating
3 chronic pain, seeing many, many different
4 scenarios. I can tell you that they are very
5 resilient, and administrative change would be
6 insignificant. They'll get the drug anyway.
7 So Schedule III indicates a dose limit of
8 15 milligrams, which was discussed. Hydrocodone is
9 an alternative to patients who do not tolerate
10 natural opioids like morphine or codeine.
11 Oxycodone is the other boundary. It's one and a
12 half times more potent than morphine. These one
13 and a half more times come from a table from
14 Goodman and Gilman, the standard textbook where
15 they rank all the narcotics against 10 milligrams
16 of morphine. Hydrocodone then is an intermediate
17 strength opioid appropriately placed, we think, in
18 C-III.
19 So it fits nicely in the spectrum of
20 medications that one can draw upon. Patients will
21 be really the primary group that will be impacted
22 with this. We expect more breakthrough pain.

1 There will be people will be writing more tablets
2 than they should, something that we don't even want
3 to consider.
4 How effective the pain management is going
5 to be questionable. If you're going to have
6 constant breakthrough pain, then, of course, the
7 patient starts to stop and starts to move around,
8 which is something we don't want to do, and then
9 the patient will be burdened, all the issues that
10 have been discussed up to now.
11 The advantages for a proposed change for us
12 and the organizations that I'm speaking for are
13 unclear, given the disadvantages to the patients in
14 pain. And the root issue -- and, of course, I
15 don't use that in the dental sense. Root issue is
16 not addressed by the schedule change. It's just
17 not addressed. I fail to see it.
18 So the risk management C-III alternative
19 codeine has more adverse effects, lower potency,
20 less consistent activity, and, of course, it's
21 inconvenient from a dental practitioner's point of
22 view. And of course, it'll be more after-hours

1 calls for alternate medication or need for a new
2 Rx.
3 So moving the HCCs from C-III to C-II is
4 really a passive act. I'm terming it actually as
5 an administrative move. The prescription drug
6 abusers will simply modify their seeking behaviors.
7 And HCCs as C-IIs, the prescribing habits may
8 change -- they probably will change -- to help
9 address issues with patient pain management, cost,
10 and inconvenience. And so C-III codeine Rx are
11 likely to increase, more pain control, and you'll
12 be getting more doses available.
13 Now, when I say by the way, NSAIDs, the
14 subtleties of the use of NSAIDs, they are not
15 maximized in pain management. And I'll just make
16 that statement. Otherwise, it can turn into a
17 pharmacology lecture. But the ADA, the American
18 Dental Association, has been very proactive in
19 passing information onto its members. Only
20 recently in July 2011, the Journal of the American
21 Dental Association had a cover story describing the
22 National Prescription Drug Abuse Prevention Plan,

1 the National Prescription Drug Take-back Initiative
2 and the Medicine Abuse Project, et cetera. So they
3 are proactive in this and sensitive.
4 The ADA is committed to prescriber education
5 as a key part of the diversion prevention. Part of
6 that -- this is a statement, but the actual active
7 part is how will we disseminate this information.
8 And that's only not here, it's really everywhere
9 because dissemination is a real issue of
10 information. And so it's really taken an
11 active -- it's been an active member in the
12 drug-free initiative, et cetera.
13 Now, the use of the Patient Provider
14 Agreement is to educate the patients on use, abuse,
15 and proper disposal is an active act that involves
16 both the prescriber and the consumer. And so we're
17 almost through with this agreement. We're going to
18 beta test it. We're going to do a pilot study.
19 And I'll tell you that the plans were to actually
20 write a grant for the Patient-Centered Research
21 Outcomes Institute to see if we can get it funded
22 to widely disseminate the PPA. And then the kind

1 of information that we get back from a community of
2 healthcare prescribers would dictate, I guess, what
3 kind of involvement the FDA wants to make it
4 mandatory, or attach it to REMS, or whatever.
5 So the patient follow-up after the Rx is
6 filled, assess efficacy and avoid overprescribing,
7 emphasize proper disposal, this is a big issue
8 because time, the time involved for all of this is
9 the number one, by the way. When we do surveys, I
10 happen to run what's called a practice-based
11 research network. You got five minutes to really
12 intercede in a physician. If it's more than five
13 minutes, you're just not going to get any time
14 back.
15 So again, the ADA supports a multitude of
16 clinical consortiums that they're involved with,
17 free online information. So they make this
18 information available to the members, and they're
19 constantly disseminating.
20 Now, they disseminate in a traditional
21 manner, but that's not -- it's just a word.
22 Information dissemination is the most complex issue

1 right now in trying to get quality information to
2 professional societies and consumers. It's not an
3 easy statement that I just made.
4 So the commitment to useful CE and opioids:
5 the judicious prescribing for legitimate pain;
6 recognizing signs that a patient may be seeking
7 prescription drugs; counseling; referring
8 chemically dependent patients for treatment; and
9 can dentists screen or be trained to identify
10 potential drug abusers for counseling. So
11 educating parents and then, et cetera, school
12 programs, it goes on and on.
13 So the conclusions, unnecessary suffering
14 for legitimate patients, we feel that it should not
15 be taken down to C-II because, as I said, it's an
16 administrative move. The effectiveness, adverse
17 effects with C-III alternatives, it may forego pain
18 meds, and self-medications will go to the ER, which
19 is something that we want to avoid. Higher out-of-
20 pocket costs and inconvenience for all the
21 statements that were said prior. And increased
22 costs, risks, inconvenience for the dentists, for

1 the prescriber, and then the unknown impact on
2 diversion, abuse and misuse.
3 So education is critical in preventing
4 diversion. Dentistry is responding. The results
5 will be publicly available as this moves forward.
6 And I thank you for your time, and thank you for
7 the opportunity to have us state our position.
8 DR. J. WOODS: Thank you, Dr. Curro.
9 Our next speaker is Jimmy Bartlett from the
10 American Optometric Association.
11 **Presentation - Jimmy Bartlett**
12 DR. BARTLETT: Thank you so much for the
13 opportunity to present before the committee today.
14 I'm representing the American Optometric
15 Association, and I want to just try not to touch on
16 too many of the redundant issues. I've sat through
17 much of today's discussion. I know the hour is
18 late, and so I'll try to move through and hit maybe
19 some novel and new ideas from an optometric
20 perspective.
21 First of all, just some brief background on
22 myself. My mother named me Jimmy so you can tell

1 where I'm from. I'm not James. I'm from the
2 South. But I just finished a 34-year academic
3 career in teaching, research and patient care at
4 the University of Alabama at Birmingham, where I
5 served as a professor and chair of the department
6 of optometry in the School of Optometry; director
7 of the professional program in optometry and also,
8 professor in the department of pharmacology and
9 toxicology of the University of Alabama School of
10 Medicine.
11 I'm a member of the US Pharmacopeia
12 representing the profession of optometry for USP,
13 and also, currently am president of PHARMAKON
14 Group. It's a consulting group for the pharma drug
15 industry. And by way of disclosure, I have no
16 conflicts of interest today. Our pharma drug
17 companies do topical therapies, nothing for pain
18 and nothing systemic.
19 This is the front page of the Birmingham
20 News, Alabama's largest newspaper, on August the
21 27th of last year. Two highlighted articles, one
22 on Tropical Storm Isaac about to hit our state.

1 The other one was about Alabama topping all other
2 states for the number of prescribed narcotics per
3 capita. And, of course, there was an article about
4 University of Alabama football team, also, but I
5 couldn't get that on the picture.
6 This article went on to talk about drug
7 diversion problem in the state of Alabama. And as
8 it turns out, I sit on our prescription drug
9 monitoring program committee. And I've seen the
10 data firsthand. We certainly are very much aware
11 of the issue of drug diversion and misuse.
12 The American Optometric Association is also
13 very much supportive of anything that we can do,
14 the approaches, the measures that we can take to
15 mitigate the problem. But we believe that
16 rescheduling hydrocodone from C-III to C-II
17 actually will have a far-reaching somewhat negative
18 impact on patient access, as I'll describe for you
19 in just a moment from an optometric point of view.
20 How much do you really know about optometry?
21 How much do you know about the profession of
22 optometry? Probably not too much, actually. But

1 let me just briefly talk about optometry and the
2 reason we believe that rescheduling from III to II
3 is not the best idea with regard to eye care in the
4 United States.
5 There are around 36,000 optometrists
6 scattered in many, many communities all across our
7 country. We're the nation's largest eye care
8 profession, serving patients in about 6500 towns,
9 cities, and counties all across the country. And
10 over half of those communities, we are the only eye
11 doctors available. You can go to states like mine,
12 and the nearest ophthalmologist, fore example, is
13 one or two hours away. And so we provide a lot of
14 what we call primary eye care all across the
15 country.
16 We are doctors of optometry. It's a
17 doctoral level profession, and we provide what we
18 really believe would be primary healthcare for the
19 eye, not just vision correction, but also, as I'll
20 describe and show you some pictures of in a moment,
21 painful conditions that are treated on a daily
22 basis by the professional doctor of optometry.

1 The last bullet on the slide here describes
2 in somewhat technical terms what the optometrist
3 does. I'll just read it very, very quickly. We
4 examine, diagnosis, treat, and manage diseases,
5 injuries and disorders of the visual system, the
6 eye and associated structures, as well as identify
7 related systemic conditions effect on the eye, such
8 as diabetes, for example, high blood pressure,
9 multiple sclerosis, rheumatoid arthritis, those
10 kind of things.
11 I actually prefer this definition. I don't
12 know if I came up with this or not a couple of
13 decades ago, but I like it. It means something to
14 me. It means something to people I talk to about
15 what is optometry. Optometrists care for most of
16 the eye problems that most people have most of the
17 time. I think that's a very straightforward
18 description of what we have been trying to do in
19 recent decades. It wasn't always the case, but
20 certainly in the last several decades, we've made a
21 very concerted effort to improve the rigorous
22 academic training of the professional doctor of

1 optometry.
2 In that respect, we're very analogous, in
3 fact, to the family medical doctor, the family
4 practitioner who treats a broad array of health
5 conditions for the population. We do the same
6 thing, but we do it for the eye. You might use the
7 adjectives usual, common, customary, ordinary kinds
8 of problems that people have, you can go to your
9 local optometrist, whether it's a refractive error
10 problem, nearsightedness, farsightedness,
11 astigmatism, presbyopia.
12 We see children. We see older patients. We
13 treat ocular diseases, things like infections of
14 the eye, bacterial conjunctivitis, viral
15 conjunctivitis, allergies, seasonal allergies.
16 Glaucoma is a very common optometric practice as
17 well as minor trauma.
18 We treat postoperative patients. Cataract,
19 as you know, is a very, very common surgical
20 procedure in this country, and optometrists team
21 together with the eye surgeon, or we may completely
22 independently see patients postoperatively during

1 the several weeks and months of care that's
2 required following cataract surgery. Very common,
3 for example, patient may be operated on at
4 Birmingham and travel back to Tuscaloosa, 50 miles
5 away, for all their follow-up care and never have
6 to go back to Birmingham to see the eye surgeon
7 postoperatively. So if the patient ends up with
8 postoperative pain, that pain needs to be managed
9 by the optometrist.
10 Some might argue that, well, if the
11 optometrist doesn't have access to Schedule II
12 opioids, why not just send the patient to the local
13 emergency department or family doctor? The problem
14 with that is instrumentation. To treat the eye to
15 properly make a diagnosis, certain specialized
16 instruments are required. A slit-lamp examination,
17 for example, is a very common procedure, and there
18 are lots of equipment and instruments utilized to
19 make a differential diagnosis.
20 I can't tell you how many foreign bodies
21 I've actually removed from patients' eyes after
22 they've been to the emergency department the day or

1 two before because the ER doctor simply didn't have
2 the instrumentation. So I'm certainly not
3 disparaging the competency of the ER doctors. It's
4 just that proper instrumentation is going to be
5 required to see the eye, which is a relatively
6 small organ, to make the diagnosis and to provide
7 the proper care.
8 So as I mentioned, the demographics of
9 optometry puts us really in the smaller
10 communities. There are many, many towns of 3,000,
11 4,000 people all across the country where there's
12 an optometrist. You won't an ophthalmologist there
13 typically, but lots of optometrists in the smaller
14 communities all across the country. We're a very
15 rural profession as well as being in the larger
16 cities. We're also scattered all through these
17 smaller, rural areas of our country, and that
18 really provides a great strength in terms of
19 patient access, access to care for our patients.
20 I've listed here on this slide briefly some
21 of the conditions that are fairly common that we
22 see in optometric practice that also are associated

1 with pain, either minor pain or moderate to severe
2 pain, some pain requiring opioids: trauma, for
3 example, foreign bodies; contusion injuries;
4 corneal abrasions, either related to not related to
5 contact lens wear; corneal ulcers; postoperative
6 pain I mentioned, either refractive surgery pain;
7 cataract surgery pain; contact lens complications,
8 overwear situations. Patients who were supposed to
9 be throwing their contacts away every day, they
10 instead wear them for a month or two, come in with
11 significant pain. Usually Friday afternoon at
12 4:30, actually, is when they come in.
13 But I wanted to show you an example or two
14 of patients who have need for short-term opioids,
15 and I think that's a real strength for us in
16 optometry. The vast majority of our patients who
17 come in with moderate to severe pain have acute
18 pain requiring short-term prescriptions, maybe two
19 or three days at a time. In fact, many states laws
20 limit the optometrist to two or three days of
21 opioid utilization. So in our profession, we're
22 not dealing at all with chronic pain, simply acute

1 pain.
2 And here's an example. This is one of my
3 patients who was chopping wood in our city. A
4 piece of wood flew up, hit the cornea. This
5 patient is in severe pain, as you might imagine.
6 And it's green because I stained it with sodium
7 fluorescein to help establish the diagnosis.
8 This is a lady who bent over and hit her eye
9 on a towel rack and lacerated the conjunctiva. She
10 has sub-conjunctiva hemorrhaging and has, of
11 course, severe pain. And, of course, I love this
12 picture. That'll wake you up. I don't have to
13 tell you that's a painful condition, and that is
14 not Photoshopped. That's an actual real patient
15 with a fishhook to the cornea.
16 Now, I noticed in reading through your
17 materials, you had some tables on the mid-level
18 practitioners and their utilization, statutory
19 privileges for the use of opioids. This is the
20 table that you should have read in your materials.
21 I'm not going to read it to you. It's simply a
22 tabulation of Schedules II through V by state in

1 alphabetical order. And you'll notice -- and I
2 have a summary slide coming up. That's all the
3 states there.
4 But just briefly, due to our time
5 consideration, here's the summary of that table.
6 We have only 10 states that statutorily permit
7 optometrists to utilize Schedule IIs. Forty-one
8 permit Schedule IIIs. So if we eliminate
9 hydrocodone from Schedule III, put it in
10 Schedule II, that will have a dramatic impact on
11 the ability of the optometrists all across the
12 country to utilize effective medication for the
13 painful conditions that our patients are presenting
14 with.
15 So ramifications for the profession of
16 optometry, some unintended consequences, the
17 primary one being we're going to remove a very
18 effective medication from our pain management
19 toolbox. And that will obviously have negative
20 consequences for our patients.
21 It represents essentially a roll back of
22 scope of practice for the optometrist. Several

1 decades ago, we were not utilizing these types of
2 medications. Now we are, and there are many, many
3 optometrists I know of who'll be very, very unhappy
4 that they can no longer utilize hydrocodone for
5 their patient management. Likewise, the patients
6 who come to see us expecting the best pain
7 management they could get anywhere in town, they
8 will be very unhappy to know that they're no longer
9 going to have access to effective pain medications
10 in the optometric office.
11 This was mentioned also. Two years ago,
12 January 2011, the FDA mandated essentially that
13 manufacturers take off the market combination
14 opioids that contained more than 325 milligrams of
15 acetaminophen, and that also is currently beginning
16 to have some impact on our practice as well.
17 So if you look at what we had just a year or
18 two ago in terms of effective pain management
19 tools, hydrocodone elixirs, syrups and solutions
20 would be disappearing if we no longer had access to
21 hydrocodone as a Schedule III medication. Solid
22 dosing units for the same medication also would be

1 disappearing. Our propoxyphene products, Schedule
2 IV as you know, have been discontinued due to
3 safety reasons. Oxycodone is not available to
4 optometrists in 41 states.
5 So it kind of leaves us with only one or two
6 products, one being the codeine combinations,
7 which, as several speakers have mentioned today,
8 are not as effective and have a less favorable side
9 effect profile. The other one listed here, you may
10 not be able to see it from where you are, it's
11 tramadol, the tramadol combination products as
12 well. So it really ties one hand behind our back
13 in terms of how we can effectively deliver pain
14 management for our patients.
15 So some possible solutions, some
16 recommendations here. Our main point that we're
17 trying to make today is that we would urge the
18 committee to recommend retaining hydrocodone in the
19 Schedule III class. We could add restrictions.
20 Maybe as a novel idea, create a subclass in
21 Schedule III, if it's legally permissible, say
22 Schedule III-A that would have restrictions a

1 little bit more so than the normal Schedule IIIs
2 but less so than Schedule IIs.
3 For example, no refills, handwritten
4 prescriptions, maybe requiring a registry of
5 prescribers and patients. Tamper-proof
6 formulations might be mandated or recommended for
7 some of these products so that we can continue
8 utilize Schedule III medications in the same class
9 for the benefit of our patients.
10 At the end of the day, what we really want
11 to do is provide the best care possible for our
12 patients. We need to do what's in the best
13 interest of our patients. And so I thank you so
14 much for your attention today.
15 DR. J. WOODS: Thank you, Dr. Bartlett.
16 Our final speaker from the professional
17 organizations is Dr. Phillip Hall from the American
18 Society for Addiction Medicine.
19 **Presentation - Phillip Hall**
20 DR. HALL: On behalf of the American Society
21 of Addiction Medicine, I'd like to thank you all
22 for undertaking such a great project and inviting

1 us to be here at the table. A little bit about me.
2 I was a family doctor from West Virginia, third
3 generation physician for about 15 years, and
4 converted over to addiction medicine. And I
5 currently run the West Virginia Medical
6 Professionals Health Program, which is a peer
7 assistance program for physicians for the state of
8 West Virginia.
9 I want to talk a little bit about the brain
10 on opioids. Most of it, you have all heard before
11 in some format. I'm not going to get into a lot of
12 detail. But, basically, the brain gets hijacked in
13 addiction, and a different part of the brain is
14 actually running the show. We do manage opioid
15 addiction quite frequently, and we actually use
16 opiates to do so.
17 There's a paradigm out there that people
18 haven't understood until recent years, and that is
19 the relationship of addiction and prescription drug
20 abuse. And when we talk about what happens,
21 there's nothing better than talking about real
22 patients. And I want to tell you a few case

1 stories that I have personally experienced related
2 to actually hydrocodone.
3 One of them is a physician 50 years old that
4 had had a stroke at age 39. He came to us in full-
5 blown opiate dependence and went to treatment.
6 Where the story started at age 39 was he had post-
7 stroke migraines, and they were treated with
8 Lortab. And over time, he adopted the philosophy
9 of having a couple of different doctors, and he was
10 getting a lot of refills, and eventually was in
11 full-blown opiate addiction as a result of
12 hydrocodone itself. And you would think a
13 physician would know better, but that's not quite
14 how it works.
15 Another one is an unemployed resident who
16 went to rehab, was doing very well and was actually
17 working in a pharmacy Her drug of choice was
18 heroin. Unfortunately, in the pharmacy when she
19 was working, she tested positive in her program for
20 hydrocodone. When we got into the story and
21 checked it out, she had actually gotten into the
22 stock bottles within the pharmacy closet, and

1 that's how she had accessed the drug leading to the
2 relapse.
3 Also, an 18-year-old friend of my daughter's
4 actually, at her graduation had gotten a tooth
5 extraction. And this one bothered me a little bit
6 because she was talking about her mother getting
7 her medication, that her teeth were hurting her.
8 And she called them hydros. And I said, "What's
9 that about?" She said, "Oh, everybody at school
10 knows about hydros." This is one of those
11 church-going girls, straight A student, who talked
12 about hydrocodone like it was some kind of pet.
13 Another one was a legislator who brought his
14 23-year-old daughter to me for heroin addiction,
15 had already flunked out of college. And in getting
16 the history from her prior to sending her away to
17 three months of rehab, she said her story started
18 in high school. And she had started taking
19 hydrocodone out of other people's medicine
20 cabinets, grandparents, aunts, uncles. But she got
21 it from her friends at school at first because it
22 made her feel good. It helped her mood, and it

1 gave her some energy.
2 Another one, physician working in an urgent
3 care, gets pneumonia, takes three courses of
4 antibiotics, prednisone and cough syrup. Over a
5 six-week course, he continued to take the
6 medication. He had refills of all three, so he
7 just refilled them. He actually saw one of his
8 partners in the hallway. And about a year later,
9 he went away to treatment for full-blown opiate
10 addiction, had been diverting drugs. And his drug
11 of choice was Tussionex, which has 10 milligrams of
12 hydrocodone per teaspoon, and this guy was taking
13 swigs out of the bottle.
14 Again, you would think a physician ought to
15 know better. And what he told me was, "It was only
16 cough syrup. I had samples." It never clicked
17 that it was a narcotic controlled substance. So if
18 physicians can't quite recognize this real clearly,
19 what about the rest of the public?
20 Sixty-year-old anesthesiologist, fentanyl
21 addict, went to rehab. Originally, he had been a
22 non-Hodgkin's lymphoma survivor, had a lot of

1 postoperative surgery due to adhesions of the
2 bowel, treated with Lortab. Over time after about
3 10 years, he did fine. Multiple surgeries, had no
4 more bowel problems. Five years later, he got a
5 divorce, marital discord, was very depressed. And
6 he remembered that Lortab made me feel better, that
7 I had some energy, I was less depressed. So he
8 started doing the Lortab again, and eventually
9 that's how he became addicted to fentanyl. Prior
10 to that, he had never used fentanyl.
11 Last Friday, a fourth-year radiology
12 resident sees me in the office. He's a paraplegic.
13 He'd been paraplegic since age 16 as a result of a
14 car injury -- car wreck involving alcohol in the
15 other driver. And he was brought to my attention
16 as a result of experimenting with marijuana and
17 some opiates and alcohol, and his wife had reported
18 him to the program director.
19 I have this guy in my office, and I'm
20 talking to him. And you can tell he's not
21 really -- he's not addicted. He is truly
22 experimenting. But when you talk to him, what you

1 realize is his adolescent social experimentation
2 phase with substances was interrupted because he
3 had a neck fracture at age 15.
4 So now that he'd gotten better and went to
5 med school, he was getting curious, and it was
6 literally his curiosity for those substances that
7 was triggered because he said, "I remember what it
8 was like taking opiates in my hospital bed. It
9 made me feel different." So this is what some of
10 our children and others go through when they get
11 that curiosity.
12 So addiction is a primary chronic disease.
13 Just like hypertension and coronary vascular
14 disease, you can have relapse, and there's negative
15 consequences.
16 I'm not going to bore you with a whole bunch
17 of facts, but the incidence is 10 to 12 percent.
18 That means 10 to 12 percent of the people in this
19 room probably have addiction. It costs a lot of
20 money, and it leads to a lot of doctor visits. The
21 number of patients that actually have to go to the
22 doctor for addiction-related issues is pretty

1 horrendous.

2 The main four Cs involve a loss of control,

3 the compulsion to get more, continued use despite

4 negative consequences and cravings. And the brain

5 doesn't care which drug it is. Whether it's

6 opiates, heroin, amphetamines, cocaine, they all

7 stimulate the same centers, kind of like the

8 carburetor of a car. Water, gas, oil in the gas

9 tank, it's all going to get gummed up.

10 So when it comes to hydrocodone versus

11 opiates, there may be differences in strengths and

12 potencies, but the addicted brain or the susceptive

13 brain can still be triggered by such things. And

14 the common denominator is dopamine. And I'm not

15 going to get into a whole bunch of that, but when

16 dopamine is up, people feel good. When dopamine is

17 down, they feel bad. And depending on the class of

18 the drug, there may be other neurotransmitters that

19 are also involved.

20 This is a very primitive way -- and I'm

21 actually going to skip this. It takes too long to

22 talk about, but it's the way I explain addiction to

1 the non-medically inclined, where the primitive
2 brain is basically in control. And when people try
3 to understand that craving for drugs and the things
4 that their family members do -- because I'm pretty
5 sure almost everybody in this room has somebody in
6 their family or close friend who suffers the
7 disease of addiction. And if I put a plastic bag
8 over our chairperson's head, he would probably
9 start acting a little bit crazy before too long.
10 And that's what people in active addiction do.
11 They will violate their own values and ethics.
12 So we know we treat pain with opiates. We
13 treat minor respiratory illness, acute and chronic
14 pain with illness, and we treat opioid dependence
15 with illness. And sometimes we go look at and ask
16 ourselves, are we enabling? Are we as a healthcare
17 system and medical community enabling addiction and
18 some of the things that go on to get worse?
19 Because in West Virginia -- and you've seen
20 enough stats today to probably kill an elephant,
21 but hydrocodone is consistently there. Either in
22 overdose deaths or prescriptions being written, it

1 is consistent throughout.
2 When I talk to the medical examiner's office
3 before I came to this conference about two weeks
4 ago, he said, "It's real simple. It's always there
5 since like 2000." It's always there since they've
6 been studying it. And again, it's involved in
7 overdose deaths related -- accident and injury
8 deaths related to suicide, homicide and
9 undetermined. But there always seems to be a
10 presence. From 2001 to 2011, again, it's always
11 been present.
12 So when you talk about Schedule II versus
13 Schedule III, when I listen to this talk and
14 everything that's been going on today, if it was
15 just up to the definition of II versus III, I think
16 we would easily roll it into Schedule II. There
17 are so many other factors at play here that I
18 didn't know about even till today that I've heard
19 that impact that decision.
20 Will it have an impact? You can't predict
21 it that I know of, but it sure is awfully
22 suspicious because I don't think our country needs

1 to prescribe 99 percent of the world's hydrocodone.
2 It's in the cabinets. These multiple refills and
3 culture sharing of what goes on, I don't see how it
4 could not have an impact, but there are a lot of
5 other things that needs taking into account.
6 Will other drugs take its place? In the
7 addicted patient, yes. Some of them may quit, but
8 they always change substances if they're forced to,
9 based on availability. We know in West Virginia,
10 heroin's been a little bit on the rise. And
11 there's some other drugs we probably might need to
12 rethink as well.
13 ASAM has a very nice public policy on
14 rethinking the whole process, and much of that has
15 been touched on today related to education,
16 storage, PDMPs. I want to point out something
17 educationally that I think is important, not just
18 the longitudinal piece because education is the
19 key. But it's not going to happen overnight.
20 But we need to do all the different tiers.
21 In other words, our children prior to exposure, our
22 children while they're being exposed to drugs, and

1 our children after they're exposed to drugs. So we
2 got to start in grade school. And we need to
3 capture the parents at this level.
4 The same with our medical students, nurses,
5 pharmacists, and the public at large. That is a
6 long ongoing process that I think, like cigarette
7 smoking, eventually had an impact. But it takes a
8 long time.
9 So what are we going to do in the meantime?
10 Well, one of the things we can consider doing is
11 rescheduling hydrocodone because it's well
12 established that hydrocodone has been present as a
13 problem for a long time.
14 Ten years ago if you had asked me what I
15 thought as a urgent care doctor who might have been
16 impacted to some degree, I'm not sure the negatives
17 at that time -- I would have told you, don't
18 reschedule. The negatives probably outweigh the
19 benefit to society. Part of that would have been
20 due to my lack of knowledge of addiction.
21 What I would ask this group to do is to make
22 society's benefit their biggest concern because all

1 these different pieces of the pie that have very
2 appropriate logical points of why not and the
3 downsides of this, I get it. I can't fix those one
4 by one, but I think cumulatively, this group and
5 everybody working together can figure out how to do
6 that because I do see hydrocodone quite frequently
7 as almost the gateway drug, like the way we used to
8 refer to marijuana.
9 People's first exposure may be through
10 legitimate medical problems, and they get that
11 memory back. And they've got all this medicine
12 around. They get exposed to it over and over. And
13 eventually, they will come back and try it again.
14 I don't understand the abuse potential pieces that
15 you-all are looking at and how you qualify that
16 with the denominator and the numerator, because I
17 got lost in that stuff.
18 What I'll tell you is the susceptible
19 patient and the addicted patient really doesn't
20 care. It's addictive. It lights them up, and it
21 leads a lot of people into worse addictions. And
22 with that, I thank you.

1 **Committee Questions to Presenters**

2 DR. J. WOODS: Thank you, Dr. Hall.

3 We now proceed to clarifying questions from
4 the committee of the professional organization
5 speakers, last item on our program for the
6 afternoon. Yes, ma'am?

7 DR. SUAREZ-ALMAZOR: Yes. I had a question
8 for Dr. Webster related to the effects of oxycodone
9 compared to hydrocodone, and that's his slide 11,
10 12 and 13, I would say. If we look at the
11 slide 11, that one does not have the dose of the
12 different drugs, oxycodone and hydrocodone, I
13 guess. Oh, yes, it does on the slide. Sorry, I
14 hadn't seen that.

15 So again, all three slides show the
16 comparative effects. However, we know that
17 oxycodone is stronger than hydrocodone. So I don't
18 think that we can really compare the effects with
19 the dosages that are shown, and I would like to
20 have that clarified.

21 Some of the speakers said that the
22 difference was .9 versus 1, and another speaker

1 said it was 50 percent stronger. So I've been
2 looking at the morphine equivalent tables, and
3 there's a little bit of a variation. But it really
4 goes from 1.2 to 1.5, I think. So this would mean
5 that the data is not comparable.
6 Also, if we go to the next slide, the
7 difference in pupil diameter again would suggest
8 that the dose of oxycodone was stronger than
9 hydrocodone as far as effects.
10 DR. WEBSTER: Yes, that's correct. I mean,
11 you have to compare something. And the ratios of
12 hydrocodone to oxycodone are arbitrary. We don't
13 know what those ratios really are. They have no
14 meaning in a chronic pain state, only in an acute
15 pain state.
16 So this is just a study that chose to use
17 milligrams to compare three different formulations
18 and take it for what it's worth. That's what it
19 is. It's milligram to milligram. And if -- that's
20 what it is. So you're just comparing milligram to
21 milligram.
22 DR. SUAREZ-ALMAZOR: Yes, but you would

1 agree that most of the literature would say that
2 it's not comparable milligram to milligram as far
3 as looking --
4 DR. WEBSTER: Twenty milligrams of analgesic
5 effect of hydrocodone is probably not equal to
6 20 milligrams of an analgesic effect of morphine or
7 of oxycodone. I don't believe that -- I mean, this
8 says 20 milligrams to 20 milligrams to 20
9 milligrams has a different -- slightly
10 different -- I'm not sure clinically
11 different -- effect on high and liking.
12 DR. SUAREZ-ALMAZOR: And I had another
13 question for Dr. Bough related to the effect that
14 rescheduling the drug for Schedule II would have on
15 long-term care. I guess that one of the concerns
16 would be that automatic refills would not be
17 available because patients are not allowed -- do
18 not have access to physicians or practitioners as
19 commonly. But the use of hydrocodone combined
20 drugs is more appropriate for acute pain
21 So I was wondering if you were talking about
22 chronic use of these combination products in long-

1 term care, which to me, would appear to be a little
2 bit of an inappropriate use, given that other
3 opioids would be more indicated for chronic pain in
4 those settings. So I was wondering if you could
5 clarify.
6 DR. BOUGH: I was referring to general use
7 of hydrocodone in the long-term care setting, not
8 trying to delineate the difference of chronic or
9 acute pain, but general use of the product within
10 the patients, depending on the patient population
11 and the treatment protocol, not trying to indicate
12 one way or the other on the pain management for
13 those patients.
14 So I don't really have an answer for your
15 question. It's just general use of the product in
16 that setting.
17 DR. J. WOODS: Dr. Nelson.
18 DR. NELSON: Thanks. For Dr. Webster, I
19 just want to clarify. I think on your slide
20 number 9, and maybe you can just explain, but using
21 death from methadone to kind minimize the potential
22 risk of oxycodone and hydrocodone is a little bit

1 unfair, I think. Everyone that takes methadone for
2 addiction for treatment reasons is already
3 addicted, and many people are taking methadone for
4 pain. And certainly a lot of the deaths that we
5 see in methadone population is in the patients who
6 are taking it for pain.
7 So what I wanted to just have you clarify
8 was the circumstances under which most of these
9 patients are dying is really not because they're
10 addicted to methadone, right? It's because the way
11 methadone is used as a pain management drug is
12 probably not perfect. It's a very difficult drug
13 to use, and it's often misused.
14 DR. WEBSTER: Well, first, I'm not
15 minimizing the toxicity, lethality of oxycodone one
16 iota. It's a very serious drug, and so is
17 hydrocodone. All of these opioids have serious
18 potential harm associated with them.
19 Now, relatively speaking, the CDC's reported
20 that one-third of all of our unintentional overdose
21 deaths are due to methadone. And it is believed
22 also that most of those deaths are in the pain

1 population, though some may not be, and that about
2 one-third, according to other data, suggest
3 one-third of those deaths occur in the first
4 10 days of the first methadone prescription.
5 So it's probably inappropriate prescribing
6 and consumption that leads to those deaths. That's
7 why their emphasis about education that's so
8 critically important. That's correct.
9 DR. NELSON: That's exactly my point. So I
10 just want to be clear that we're not really using
11 methadone as a comparator as to why these drugs are
12 not addictive, especially looking at death and not
13 addiction isn't really a fair comparison.
14 DR. WEBSTER: Yes, you're correct. I agree
15 absolutely.
16 DR. J. WOODS: Dr. Morrato.
17 DR. MORRATO: Thank you. I had a follow-up
18 clarification question for Dr. Webster as well as
19 Dr. Bough and Simenson. Both of you I thought did
20 a very nice job delineating sort of the potential
21 consequences of up-scheduling. I was wondering if
22 your respective associations have taken a formal

1 position on whether they're in favor or opposed to
2 the proposal that we're considering.
3 DR. WEBSTER: The American Academy of Pain
4 Medicine is not taking a formal -- well, our formal
5 position is the following, that we're neither in
6 support or nor in opposition to rescheduling of
7 hydrocodone. It is our hope that the FDA, with
8 your input and the input of the broader community,
9 will take into consideration all of the great
10 information and come up with a very thoughtful
11 decision.
12 (Laughter.)
13 DR. BOUGH: Not to repeat that, the American
14 Pharmacists Association chose not to make an
15 official position. Our goal was to provide
16 information to help educate and raise awareness of
17 the issues you should consider as a committee, but
18 we'll rely on the final decision of FDA as you
19 evaluate all of the options. But we've chosen just
20 to monitor the activity.
21 DR. MORRATO: So in light of that, I was
22 interested in the Missouri -- I mean, the Minnesota

1 findings. Do you have any data around the
2 effectiveness of what's happening in Minnesota? I
3 know we've heard data that's been multistate from
4 various sources, but I didn't know if you being on
5 the cutting edge of the program --
6 MR. SIMENSON: As to the PDMP or inter-
7 collaboration?
8 DR. MORRATO: Yes. And the collaboration as
9 well.
10 MR. SIMENSON: The PDMP has been effective
11 in our practice. We see almost zero drug seeking
12 behavior in patients coming from all over a big
13 area trying to find somewhere where they could get
14 their medication because you can check on that if
15 you have the slightest suspicion of what their
16 history is. I think that's been extremely
17 effective, and we wouldn't think of not using it.
18 And as far as the inter-professional working
19 with other prescribers and other healthcare
20 providers, I think we've seen 20 percent of these
21 chronic opioid patients have either had their
22 therapy changed or had it discontinued after they

1 started spending more time with the patient. And
2 whether it was the information the pharmacy
3 provided or whether it was that longer period of
4 time that the physician or nurse practitioner spent
5 with the patient, I think it's a combination of the
6 two that you're not going to let the other person
7 down. And it's easier to make a decision that's
8 hard to make in some cases. So I would say it's
9 effective, very effective.
10 DR. MORRATO: Thank you.
11 DR. J. WOODS: Dr. Smith.
12 DR. SMITH: Given the recent challenges with
13 medication backorders by wholesalers and
14 manufacturers, has the FDA, DEA, or the American
15 Pharmacy Association examined or build a proactive
16 model in the event of a disruption of the inventory
17 stream of hydrocodone combinations or alternatives
18 with the proposed rescheduling?
19 DR. BOUGH: It's one of the -- so the
20 challenge of potential disruption in the supply
21 chain and access to hydrocodone-containing
22 products, there could be issues with drug shortage

1 because of supply chain logistics and inventory of
2 the product. Often, wholesalers and pharmacies
3 don't carry a lot of extra inventory of C-IIs.
4 There may be a little more leeway with C-IIIs.
5 So I think there might be availability of
6 the product, but it might not be in the store at
7 that hour. And it might be next-day order, two-
8 day, and that would be a patient delay, especially
9 in acute care treatment.
10 MR. SIMENSON: And also, one of the other
11 concerns about that is once it's a Schedule II, the
12 DEA works very carefully with manufacturers, as I
13 understand, allowing them to have a set amount of
14 raw material on hand. And we do experience at the
15 pharmacy level at the end of the year, on a fairly
16 regular basis -- this year wasn't as bad as some of
17 the previous years, but the manufacturers made all
18 the medications that they can out of their raw
19 materials, and there is a shortage for a short
20 period of time.
21 There are lots of talk on the wholesaler
22 level and FDA and other places about getting

1 surpluses of material into areas where there are
2 shortages. There's monitoring systems. But the
3 biggest cause of raw material shortages are a plant
4 being shut down because of bad manufacturing
5 processes, and I don't think anybody can do
6 anything about that.
7 DR. J. WOODS: Ms. Phillips.
8 MS. PHILLIPS: This is a clarifying question
9 for Dr. Curro related to the dental practice. You
10 indicated that the primary use your practitioners
11 would have for these agents is in acute pain and
12 just a couple of days. So I was unclear about the
13 need for refills.
14 I guess my question related to this is, if
15 there was ready access to e-prescribing to allow a
16 dentist to take care of an acute pain setting over
17 a weekend or something that came up until they
18 could be seen in the office, would that alleviate a
19 lot of the issues with -- you really don't have a
20 lot of issues of refills if you're dealing with an
21 acute pain situation such as you described.
22 DR. CURRO: And I would agree with that, and

1 that would be a good practice. And most of the
2 pain in dentistry is acute. Unless you're treating
3 neuralgias or other kinds of syndromes, as I said
4 years ago, that we wouldn't use an opioid. Yes,
5 but now we do.
6 So that's really should be a small
7 percentage of the profession. Most of the pain is
8 acute, and, as I said, probably the convenience of
9 over prescribing. There is a convenience factor
10 here, as you said, about weekends, calls,
11 et cetera. And I think in general, there's a
12 tendency, at least from what we're finding from the
13 surveys that we're doing, to try and accommodate a
14 patient. I just hesitated for a moment because in
15 this new environment of patient centeredness, it
16 actually could get worse. I just thought about it.
17 So it can be an issue. But again, it goes
18 back to education and the amount of pain that you
19 initiate in an acute pain syndrome in a surgery
20 situation, at least in the area that we operate in,
21 depends upon a host -- how long you keep the bone
22 exposed, is it dry, et cetera, et cetera. So it

1 really is an individual assessment.
2 DR. J. WOODS: Dr. Kaboli.
3 DR. KABOLI: Actually, I had the same
4 question, so you can take my name off.
5 DR. J. WOODS: Dr. Maxwell.
6 DR. MAXWELL: A quick question for Dr. Hall.
7 Maybe I missed it. Has the American Society on
8 Addiction Medicine taken a position on this?
9 DR. HALL: They sent a letter to this
10 committee within the last year recommending strong
11 consideration -- it was under Dr. Gitlow -- to
12 reschedule the hydrocodone. We don't have a
13 separate ASAM policy like we do on the prescription
14 diversion targeting that one item, but there was a
15 letter sent in favor.
16 DR. J. WOODS: Dr. Crawford.
17 DR. CRAWFORD: Thank you. This question is
18 also for Dr. Hall. So I'm looking at your slide 20
19 on the popular painkillers in West Virginia. I
20 guess I'll even broaden it to say you can either
21 speak in terms of West Virginia or your knowledge
22 more broadly nationally, because you were saying

1 hydrocodone is always in the top five for the group
2 that's monitoring the use. This is on per capita
3 consumption, but under that one, that little
4 footnote underneath, it talks about abuse.
5 So with respect to hydrocodone used with
6 your expertise, what would be your best learned
7 guess or opinion about how much of hydrocodone
8 combination product use is due to legitimate
9 therapeutic use versus misuse or abuse?
10 DR. HALL: I can't quantify that myself with
11 exact percentages. I can tell you that most
12 addicted patients I deal with that have opiate
13 addiction, at some point in time, one of two things
14 happened. They had a legitimate medical problem.
15 I had an orthopedic doctor that broke his leg
16 before it's all said and done. So legitimate
17 medical problems leading to full-blown addition or
18 the experimental use in our kids, which is what's
19 been a little bit more concerning for me because
20 that part of the population that I'm seeing that
21 suffer full-blown addiction at younger ages and
22 failing out of college is a lot higher.

1 So it appears to be significant and
2 increasing.
3 DR. J. WOODS: Ms. May.
4 MS. MAY: This is for Dr. Hall. You
5 mentioned -- well, actually, many people have
6 mentioned that if a person's drug -- addicted to a
7 particular drug, for example, a hydrocodone
8 combination and they don't have access to it, that
9 they'll probably seek another type of drug, either
10 opiate or benzodiazepine, or possibly even illicit
11 drug on the street.
12 So how would you say rescheduling the drug
13 would decrease this drug-seeking behavior of an
14 addict?
15 DR. HALL: In full-blown addiction patients
16 who hydrocodone is their drug of choice and you
17 take it from them, it probably won't change what
18 they do. Some of them may cold turkey and quit,
19 but the full-blown addiction patients are the ones
20 that are a little less susceptible to the benefits
21 of rescheduling. It's the opiate naive part of our
22 population that hasn't been exposed to opiates and

1 developed addiction, or has been exposed at some
2 point in time and turns to the cabinet years later
3 because it's still in there with three more
4 refills.
5 So in the addicted patient, I'm not sure how
6 big of a difference that will make, but it's the
7 rest of our population, because this incidence is
8 not going down. It's rising.
9 MS. MAY: I may have missed this, but there
10 was -- any way of quantifying the percentage of
11 people that are prescribed the medication for an
12 acute pain are ones that tend to become abusers of
13 the hydrocodone combination?
14 DR. HALL: I'm sorry. I missed your
15 question.
16 MS. MAY: Are the patients that are
17 prescribed -- is there any information about the
18 patients that are prescribed the hydrocodone
19 combination medication for acute pain, how many
20 people end up being addicted to the medications?
21 Because you've mentioned this seems to be the first
22 line drug.

1 DR. HALL: I don't have a number to tell you
2 how many of the combination hydrocodone products
3 get addicted. It just sort of appears to be over
4 time that it's increasing, and it's functioning
5 almost like a gateway drug for the younger
6 population.
7 MS. MAY: But I guess my question is, if you
8 moved that drug, then wouldn't there be another
9 gateway drug?
10 DR. HALL: Beg your pardon?
11 MS. MAY: If you rescheduled that drug,
12 wouldn't there ultimately be another gateway drug?
13 DR. HALL: I don't know the answer to that.
14 I can't predict the future. But I can tell you
15 that with the epidemic we're facing nationally and
16 everything that we're trying to do with education
17 and PMPs and being right here, I do not think
18 rescheduling hydrocodone combination products is
19 going to hurt that effort. If anything, it very
20 may well accelerate the educational process because
21 it sure has brought a whole bunch of people to the
22 table just to come talk about it, and that's a good

1 thing.

2 MS. MAY: Thank you.

3 DR. J. WOODS: A final one there.

4 MS. LANDIS: Just a question while you're up

5 there, Dr. Hall. On your slide that looked at drug

6 overdose deaths, the alprazolam was up there higher

7 than anything else in 2011. This meeting today is

8 about rescheduling of hydrocodone from a III to a

9 II. In your opinion, from your expertise, do you

10 see the need for other drugs to be moved?

11 DR. HALL: Yes, I do. I've got a good

12 pharmacy friend down in Tennessee. We have this

13 discussion a lot. And if you-all want some help

14 doing it, we can do it for you. But it would take

15 us about a year to sit down and just go through the

16 list because there's a lot on the list I don't

17 understand. Historically now, I do. I get it. It

18 was 30 years ago, and a legislative mandate was

19 part of it.

20 But Ultram, Xanax, carisoprodol, nalbuphine,

21 some others, you look at Fiorinal and Fioricet,

22 those are in two different classes, based on what

1 the additional is in there. So, yes, there's a
2 whole bunch others I think we could look at.
3 MS. LANDIS: So from your background, I'm
4 almost hearing that the scheduling system we have
5 and the medications in the schedules are inadequate
6 and is the cause maybe of all of the addictions or
7 part of the causes.
8 DR. HALL: I would be hesitant to use that
9 strong a term as "inadequate." Let's say there
10 could be room for improvement. And the cause for
11 the addiction epidemic is multifactorial. So we
12 can't blame any one piece of this, but it has
13 contributed.
14 MS. LANDIS: One more question, if you take
15 hydrocodone off the table completely for those that
16 are involved in addiction, what is going to be
17 their choice of drug?
18 DR. HALL: You got a crystal ball? I assume
19 it would either be an opiate for those who are
20 addicted to opiates, and I'm not sure about the
21 opiate naive and yet to be exposed population.
22 Maybe it would go back to being alcohol, marijuana.

1 MS. LANDIS: So regardless, those with
2 addiction problems, it's -- there is going to be
3 something else out there for them?
4 DR. HALL: Addiction is a disease that
5 occurs at an incidence rate, so we're not going to
6 annihilate the disease of addiction by rescheduling
7 hydrocodone. I think we may better manage some of
8 those who are addicted or yet to be addicted by
9 doing that.
10 DR. J. WOODS: Dr. Nelson.
11 DR. NELSON: So I just had a question for
12 the American Pharmacy Association. I'm not one
13 that usually does a lot of fact checking, but I
14 just happened to come across a letter written by
15 your organization to Senator Manchin's office,
16 which opposed the rescheduling. So maybe it's
17 changed because this was done in May, so maybe
18 things have changed.
19 DR. BOUGH: Yes. We did sign a joint letter
20 with a variety of pharmacy organizations. What we
21 opposed was the process that the potential
22 rescheduling was moving through as a congressional

1 amendment to legislation. This is the process that
2 we support to consider rescheduling. We didn't
3 like -- we were concerned with how it was moving
4 forward legislatively.

5 **Adjournment**

6 DR. J. WOODS: I want to thank everybody for
7 a very spirited discussion today, very nice set of
8 presentations, and some good questions of the
9 committee and an attentive audience.
10 I would like for the members of the
11 committee to be sure to take their folders home
12 with them. Anything that you don't want to, leave
13 here, but anything you want to use later on
14 tomorrow, please take it with you.
15 Remember that there's no discussion outside
16 the room about the matters associated with our
17 decisions, and we will adjourn now and start again
18 tomorrow morning at 8:00. Whoever said no one
19 works in Washington?
20 (Whereupon, at 5:51 p.m., the meeting was
21 concluded.)
22