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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
JOINT MEETING OF THE ANESTHETIC AND ANALGESIC
DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC)
AND THE DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE (DSaRM) AND THE
PEDIATRIC ADVISORY COMMITTEE (PAC)

Friday, September 16, 2016

8:07 a.m. to 2:39 p.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31 Conference Center
The Great Room (Rm. 1503)
Silver Spring, Maryland

1 **Meeting Roster**

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

3 **Stephanie L. Begansky, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY**

9 **COMMITTEE MEMBERS (Voting)**

10 **Brian T. Bateman, MD, MSc**

11 Associate Professor of Anesthesia

12 Division of Pharmacoepidemiology and

13 Pharmacoeconomics

14 Department of Medicine

15 Brigham and Women's Hospital

16 Department of Anesthesia, Critical Care, and Pain

17 Medicine

18 Massachusetts General Hospital

19 Harvard Medical School

20 Boston, Massachusetts

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1 **Raeford E. Brown, Jr., MD, FAAP**

2 *(Chairperson)*

3 Professor of Anesthesiology and Pediatrics

4 College of Medicine

5 University of Kentucky

6 Lexington, Kentucky

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8 **David S. Craig, PharmD**

9 Clinical Pharmacy Specialist

10 Department of Pharmacy

11 H. Lee Moffitt Cancer Center & Research Institute

12 Tampa, Florida

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14 **Charles W. Emala, Sr., MS, MD**

15 Professor and Vice-Chair for Research

16 Department of Anesthesiology

17 Columbia University College of Physicians &

18 Surgeons

19 New York, New York

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1 **Anita Gupta, DO, PharmD**

2 *(via telephone on day 1)*

3 Vice Chair and Associate Professor

4 Division of Pain Medicine & Regional

5 Anesthesiology

6 Department of Anesthesiology

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8 Philadelphia, Pennsylvania

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10 **Jennifer G. Higgins, PhD**

11 *(Consumer Representative)*

12 Director of Strategic Planning and Business

13 Development

14 Center for Human Development

15 Springfield, Massachusetts

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17 **Alan D. Kaye, MD, PhD**

18 Professor and Chairman

19 Department of Anesthesia

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21 New Orleans, Louisiana

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11 College of Public Health

12 The Ohio State University

13 Columbus, Ohio

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1 **ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY**

2 **COMMITTEE MEMBER (Non-Voting)**

3 **W. Joseph Herring, MD, PhD**

4 *(Industry Representative)*

5 Neurologist

6 Executive Director and Section Head

7 Neurology, Clinical Neurosciences

8 Merck Research Laboratories, Merck & Co.

9 North Wales, Pennsylvania

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

12 **MEMBERS (Voting)**

13 **Tobias Gerhard, PhD, RPh**

14 Associate Professor

15 Rutgers University

16 Department of Pharmacy Practice and

17 Administration

18 Ernest Mario School of Pharmacy

19 New Brunswick, New Jersey

20

21

22

1 **Linda Tyler, PharmD, FASHP** *(via telephone)*
2 Chief Pharmacy Officer
3 Administrative Director, Pharmacy Services
4 University of Utah Health Care
5 Professor (Clinical) and Associate Dean for
6 Pharmacy Practice
7 University of Utah College of Pharmacy
8 Salt Lake City, Utah

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10 **PEDIATRIC ADVISORY COMMITTEE MEMBERS (Voting)**

11 **Mary Cataletto, MD, FAAP**

12 Attending Physician
13 Winthrop University Hospital
14 Professor of Clinical Pediatrics
15 SUNY Stony Brook
16 Stony Brook, New York

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18 **Avital Cnaan, PhD**

19 Children's National Medical Center
20 Washington, District of Columbia

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22

1 **Melody Cunningham, MD**

2 Medical Director

3 Palliative Medicine Service

4 Le Bonheur Children's Hospital

5 Associate Professor of Pediatrics

6 University of Tennessee, Medical School

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9 **Robert Dracker, MD, MBA, MHA**

10 Director, Summerwood Pediatrics

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14 **Peter Havens, MD, MS**

15 Director, Pediatric HIV Care Program

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17 Professor, Pediatrics

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16 **Christy Turer, MD, MHS, FAAP, FTOS**

17 Assistant Professor, Pediatrics,
18 Clinical Sciences and Medicine
19 Director, General Academic Pediatrics Fellowship
20 UT Southwestern and Children's Medical Center
21 Dallas, Texas

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Kelly Wade, MD, PhD

Attending Neonatologist
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Michael White, MD, PhD

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PEDIATRIC ADVISORY COMMITTEE MEMBERS (Non-Voting)

Bridgette Jones, MD

(Healthcare Representative)
Pediatric Health Organization Representative
Associate Professor of Pediatrics and Medicine
Children's Mercy Hospital
Kansas City, Missouri

1 **Samuel D. Maldonado, MD, MPH, FAAP**

2 *(Industry Representative)*

3 Vice-President and Head
4 Pediatric Drug Development
5 Center of Excellence
6 Johnson & Johnson PRD
7 Raritan, New Jersey

8
9 **TEMPORARY MEMBERS (Voting)**

10 **Sean P. Alexander, MD**

11 Director of Inpatient Medicine
12 Medical Director, Pain Medicine Care Complex
13 Sheikh Zayed Institute
14 Children's National Health System
15 Washington, District of Columbia

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17 **Stephanie Crawford, PhD, MPH**

18 Professor, Department of Pharmacy Systems,
19 Outcomes and Policy
20 Professor, Department of Medical Education
21 University of Illinois at Chicago
22 Chicago, Illinois

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Angela S. Czaja, MD MSc

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1 **Arthur F. Harralson, PharmD, BCPS**

2 Professor of Pharmacogenomics and
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4 Shenandoah University and
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10 **Arthur H. Kibbe Ph.D.**

11 Emeritus Professor of Pharmaceutical Sciences
12 Nesbit School of Pharmacy
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16 **Tamar Lasky, PhD, FISPE**

17 Owner/Consultant
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1 **Lynne G. Maxwell, MD**

2 Associate Director

3 Division of General Anesthesiology

4 The Children's Hospital Philadelphia

5 Associate Professor of Anesthesiology and

6 Critical Care

7 Perelman School of Medicine

8 University of Pennsylvania

9 Philadelphia, Pennsylvania

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11 **Melanie Dawn Nelson, PhD**

12 *(Patient Representative)*

13 Mount Pleasant, Michigan

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15 **Kathleen A. Neville, M.D., M.S., M.B.A**

16 Professor of Pediatrics, University of Arkansas for

17 Medical Sciences

18 Chief, Section of Clinical Pharmacology and

19 Toxicology

20 Arkansas Children's Hospital

21 Little Rock, Arkansas

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1 **Stephen W. Patrick, MD, MPH, MS**

2 Assistant Professor, Pediatrics and Health Policy

3 Division of Neonatology

4 Vanderbilt University School of Medicine

5 Nashville, Tennessee

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7 **Anne-Michelle Ruha, MD**

8 Medical Toxicology Fellowship Director

9 Clinical Associate Professor, Department of

10 Emergency Medicine

11 University of Arizona College of Medicine

12 Phoenix

13 Phoenix, Arizona

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15 **Gary A. Walco, PhD**

16 Professor of Anesthesiology & Pain Medicine

17 Adjunct Professor of Pediatrics and Psychiatry

18 University of Washington School of Medicine

19 Director of Pain Medicine

20 Seattle Children's Hospital

21 Seattle, Washington

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1 **FDA PARTICIPANTS (Non-Voting)**

2 **Sharon Hertz, MD**

3 Director

4 Division of Anesthesia, Analgesia and Addiction

5 Products (DAAAP)

6 Office of Drug Evaluation II (ODE-II)

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

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9 **Judy Staffa, PhD, RPh**

10 Acting Associate Director for Public

11 Health Initiatives

12 Office of Surveillance and Epidemiology (OSE)

13 CDER, FDA

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15 **Ellen Fields, MD, MPH**

16 Deputy Director

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

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19 **Robert "Skip" Nelson, MD PhD**

20 Deputy Director and Senior Pediatric Ethicist

21 Office of Pediatric Therapeutics

22 Office of the Commissioner, FDA

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Lynne Yao, MD

Director
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV (ODE-IV)
OND, CDER, FDA

LCDR Grace Chai, PharmD

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Division of Epidemiology II (DEPI- II)
Office of Pharmacovigilance and Epidemiology
(OPE), OSE, CDER, FDA

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

2 (8:07 a.m.)

3 **Call to Order**

4 **Introduction of Committees**

5 DR. BROWN: We're going to go ahead and get
6 started. I'd like to remind everyone to please
7 silence your cell phones, smartphones, and any
8 other devices, if you have not already done so. I
9 would also like to identify the FDA press contact,
10 Sarah Peddicord, who is not in the back.

11 My name is Raeford Brown. I'm the
12 chairperson of the Anesthetic and Analgesic Drug
13 Products Advisory Committee. I'll be chairing this
14 meeting.

15 I will now call the joint meeting of the
16 Anesthetic and Analgesic Drug Products Advisory
17 Committee, the Drug Safety and Risk Management
18 Advisory Committee, and the Pediatric Advisory
19 Committee to order. We'll start by going around
20 the table and introduce ourselves, and we're going
21 to start today with Dr. Staffa, down here at the
22 FDA end.

1 DR. STAFFA: Good morning. I'm Judy Staffa.
2 I'm the associate director for public health
3 initiatives in the Office of Surveillance and
4 Epidemiology, in CDER at FDA.

5 DR. HERTZ: Sharon Hertz, director, Division
6 of Anesthesia, Analgesia, and Addiction Products.

7 DR. FIELDS: Ellen Fields, deputy director
8 in the same division.

9 DR. NELSON: Skip Nelson, deputy director,
10 Office of Pediatric Therapeutics.

11 DR. CHAI: Lieutenant Commander Grace Chai,
12 deputy division director for drug utilization in
13 Division of Epidemiology II, OSC CDER.

14 DR. CZAJA: Angela Czaja, a pediatric
15 critical care physician at Children's Hospital of
16 Colorado.

17 DR. MAXWELL: Lynne Maxwell, pediatric
18 anesthesiologist, Children's Hospital at
19 Philadelphia; temporary member of the Pediatric
20 Advisory Committee.

21 DR. WALCO: Gary Walco, Department of
22 Anesthesiology, University of Washington.

1 DR. FLICK: Randall Flick, pediatric,
2 anesthesia, critical care, Mayo Clinic.

3 DR. SHOBEN: Abi Shoben, associate professor
4 of biostatistics at the Ohio State University.

5 DR. TURER: Christy Turer, combined internal
6 medicine, pediatrics at the University of Texas
7 Southwestern, and member of the Pediatric Advisory
8 Committee.

9 DR. CNAAN: Avital Cnaan, biostatistician,
10 Children's National Health Center and GW University
11 at Washington, D.C., member of the Pediatric
12 Advisory Committee.

13 DR. HUDAK: Mark Hudak, chair of pediatrics,
14 University of Florida College of Medicine,
15 Jacksonville, and chair of the PAC.

16 DR. GUPTA: Dr. Anita Gupta. I'm vice chair
17 and associate professor of anesthesiology and pain
18 medicine at Drexel University College of Medicine.

19 DR. WHITE: Michael White, pediatric
20 cardiologist from the Ochsner Health System and
21 Ochsner Clinical School, and a member of the PAC.

22 DR. BATEMAN: Brian Bateman,

1 anesthesiologist, Massachusetts General Hospital,
2 and member of the Anesthetic and Analgesic Advisory
3 Committee.

4 DR. EMALA: Charles Emala, anesthesiologist
5 and vice chair for research, Department of
6 Anesthesiology at Columbia University.

7 DR. BEGANSKY: Stephanie Begansky. I'm the
8 designated federal officer for today's meeting.

9 DR. BROWN: And I'm Rae Brown. I'm a
10 pediatric anesthesiologist at University of
11 Kentucky Medical Center.

12 DR. KAYE: Good morning. I'm Alan Kaye.
13 I'm an anesthesiologist, pain specialist and
14 pharmacologist, and I am a program director and
15 chairman at the LSU School of Medicine in New
16 Orleans, Louisiana.

17 DR. GERHARD: Tobias Gerhard, Rutgers
18 University, pharmacoepidemiologist and member of
19 the Drug Safety and Risk Management Advisory
20 Committee.

21 DR. HARRALSON: Art Harralson, associate
22 dean for research, Shenandoah University and the

1 George Washington University, and I'm a consultant.

2 DR. WADE: Kelly Wade, neonatologist for
3 Children's Hospital of Philadelphia and the
4 University of Pennsylvania Medical School, member
5 of the PAC.

6 DR. MCCANN: Mary Ellen McCann, pediatric
7 anesthesiologist at Boston Children's Hospital.

8 DR. PATRICK: Stephen Patrick, neonatologist
9 at Vanderbilt University School of Medicine.

10 DR. CRAIG: David Craig. I'm a clinical
11 pharmacist specialist at Moffitt Cancer Center.

12 DR. HIGGINS: Jennifer Higgins. I'm the
13 consumer representative to AADPAC.

14 DR. NELSON: Dawn Nelson. I'm a professor
15 of audiology at Central Michigan University, but in
16 this capacity, I'm a patient representative. My
17 daughter has sickle cell anemia.

18 DR. NEVILLE: Kathleen Neville. I'm a
19 clinical pharmacologist and pediatric
20 hematologist/oncologist at Arkansas Children's, and
21 I'm a consultant.

22 DR. CATALETTO: Mary Cataletto. I'm a

1 pediatric pulmonologist at Winthrop University
2 Hospital, and a member of the PAC.

3 DR. HOEHN: Sarah Hoehn, pediatric critical
4 care at University of Kansas, member of the
5 Pediatric Advisory Committee.

6 DR. HAVENS: Peter Havens, pediatric
7 infectious diseases at Children's Hospital of
8 Wisconsin, and the Medical College of Wisconsin in
9 Milwaukee, Wisconsin, and a member of the PAC.

10 DR. JONES: I'm Bridgette Jones. I'm an
11 allergy immunologist and pediatric clinical
12 pharmacologist at Children's Mercy Hospital in
13 Kansas City. I'm the AAP representative on the
14 PAC.

15 DR. KIBBE: Art Kibbe. I'm an emeritus
16 professor of pharmaceuticals and pharmacokinetics,
17 Wilkes University Nesbit School of Pharmacy, and
18 I'm serving today on the Pediatric Advisory
19 Committee.

20 DR. LASKY: Tammy Lasky. I'm an
21 epidemiologist. I work as a consultant. And today
22 I'm a temporary member of the Pediatric Advisory

1 Committee.

2 DR. RUHA: Hi. I'm Michelle Ruha. I am a
3 medical toxicologist from Banner University Medical
4 Center in Phoenix, and I am a temporary member of
5 the Drug Safety and Risk Management Advisory
6 Committee.

7 DR. CRAWFORD: Good morning. Stephanie
8 Crawford, professor, University of Illinois at
9 Chicago College of Pharmacy. I am not a member of
10 the PAC. I am a temporary consultant for the Drug
11 Safety and Risk Management Advisory Committee,
12 DSaRM.

13 DR. MALDONADO: I'm Sam Maldonado. I'm an
14 industry representative to the Pediatric Advisory
15 Committee.

16 DR. HERRING: Good morning. I'm
17 Joe Herring, a neurologist, executive director of
18 clinical neuroscience at Merck and industry
19 representative to the AADPAC.

20 DR. BROWN: Welcome to each and every one of
21 you. We appreciate the fact that you're here and
22 taking time out of your busy professional schedules

1 to help us with some very important topics.

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 is that today's meeting will be a fair and
6 open forum for discussion of these issues, and that
7 individuals can express their views without
8 interruption. Thus, as a gentle reminder,
9 individuals will be allowed to speak into the
10 record only if recognized by the chair. We look
11 forward 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 this meeting with the
22 media until its conclusion. Also, the committee is

1 reminded to please refrain from discussing the
2 meeting topic during breaks or lunch.

3 Now I'll pass it to Lieutenant Commander
4 Stephanie Begansky, who will read the Conflict of
5 Interest Statement.

6 **Conflict of Interest Statement**

7 DR. BEGANSKY: Thank you.

8 Good morning. The Food and Drug
9 Administration is convening today's joint meeting
10 of the Anesthetic and Analgesic Drug Products
11 Advisory Committee, Drug Safety and Risk Management
12 Advisory Committee, and the Pediatric Advisory
13 Committee, under the authority of the Federal
14 Advisory Committee Act of 1972.

15 With the exception of the industry
16 representatives, all members and temporary voting
17 members of the committees are special government
18 employees or regular federal employees from other
19 agencies, and are subject to Federal conflict of
20 interest laws and regulations.

21 The following information on the status of
22 these committees' compliance with federal ethics

1 and conflict of interest laws, covered by but not
2 limited to those found at 18 U.S.C. Section 208, is
3 being provided to participants in today's meeting
4 and to the public. FDA has determined that members
5 and temporary voting members of these committees
6 are in compliance with federal ethics and conflict
7 of interest laws.

8 Under 18 U.S.C. Section 208, Congress has
9 authorized FDA to grant waivers to special
10 government employees and regular federal employees
11 who have potential financial conflicts when it is
12 determined that the agency's need for a particular
13 individual's services outweighs his or her
14 potential financial conflict of interest, or when
15 the interest of a regular federal employee is not
16 so substantial as to be deemed likely to affect the
17 integrity of the services which the government may
18 expect from the employee.

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

1 well as those imputed to them, including those of
2 their spouses or minor children, and for purposes
3 of 18 U.S.C. Section 208, their employers. These
4 interests may include investments; consulting;
5 expert witness testimony; contracts, grants,
6 CRADAs; teaching, speaking, writing; patents and
7 royalties; and primary employment.

8 Today's agenda involves discussion of the
9 appropriate development plans for establishing the
10 safety and efficacy of prescription opioid
11 analgesics for pediatric patients, including
12 obtaining pharmacokinetic data and the use of
13 extrapolation. This is a particular matters
14 meeting during which general issues will be
15 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 meeting.

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 Dr. Bridgette Jones is participating in this
4 meeting as the health care representative, and that
5 is a non-voting position.

6 With respect to FDA's invited industry
7 representatives, we would like to disclose that
8 Drs. William Herring and Samuel Maldonado are
9 participating in this meeting as nonvoting industry
10 representatives, acting on behalf of regulated
11 industry. Dr. Herring's and Maldonado's roles at
12 this meeting are to represent industry in general
13 and not any particular company. Dr. Herring is
14 employed by Merck and Co., and Dr. Maldonado is
15 employed by Johnson & Johnson.

16 With regard to FDA's guest speakers, the
17 agency has determined that the information to be
18 provided by these speakers is essential. The
19 following interests are being made public to allow
20 the audience to objectively evaluate any
21 presentation and/or comments made by the speakers.

22 Dr. Steven Weissman has acknowledged that he

1 owns shares of Johnson & Johnson and Merck stock.
2 In addition, he has past and current involvements
3 as an investigator on several studies for pediatric
4 pain management, including a Grunenthal pediatric
5 trial of tapentadol, The Medicines Company
6 pediatric trial of Ionsys, and a Purdue pediatric
7 trial of OxyContin. He also previously served as a
8 member of the Purdue Pediatric Advisory Board for
9 oxycodone and buprenorphine. As a guest speaker,
10 Dr. Weisman will not participate in committee
11 deliberations, nor will he vote.

12 We would like to remind members and
13 temporary voting members that if the discussions
14 involve any other topics not already on the agenda
15 for which an FDA participant has a personal or
16 imputed financial interest, the participants will
17 need to exclude themselves from such involvement,
18 and their exclusion will be noted for the record.
19 FDA encourages all other participants to advise the
20 committees of any financial relationships that they
21 may have regarding the topic that could be affected
22 by the committees' discussions. Thank you.

1 DR. BROWN: We'll now proceed with the FDA's
2 opening remarks from Dr. Sharon Hertz.

3 **FDA Introductory Remarks - Sharon Hertz**

4 DR. HERTZ: Good morning. Welcome back to
5 all of you. I'm really looking forward to today's
6 discussion. Dr. Brown, members of the Anesthesia
7 and Analgesia Drug Product Advisory Committee, the
8 Drug Safety and Risk Management Advisory Committee,
9 and the Pediatric Advisory Committee, and invited
10 guests, the second day of this very important
11 meeting will be very interesting as we take into
12 consideration some of the extremely interesting
13 discussions or presentations that we heard
14 yesterday.

15 We had a number of informative and
16 thought-provoking presentations spanning the
17 regulations and laws in place supporting the
18 development of drug products for pediatric
19 patients, the existing patterns of drug use. We
20 heard a lot about how FDA has approached this area
21 of drug development and some of the challenges.

22 We have gotten information about the

1 management of pain in children, and how we must
2 continue to recognize, I think most people here do,
3 that pediatric patients is not an entity, that
4 children represent a broad stakeholder group, if
5 you will, a broad population with individual needs
6 based on stages of development.

7 We also heard a lot of very interesting
8 information about specific uses of opioids in
9 managing pain; some of the challenges as we
10 continue to try and get pediatric-specific
11 information from studies; some of the factors that
12 underlie risk for misuse and addiction in
13 adolescents; and we heard discussion of an ethical
14 framework that we can use for considering the
15 impact of our decisions with regard to individual
16 versus public health needs.

17 I would like to ask us to try to hold the
18 initial clarifying questions to true clarifying
19 questions that will wrap up any questions left from
20 yesterday. We'll then go into our open public
21 hearing, and then we will proceed to a discussion
22 of many questions, which we'll come back and

1 present.

2 I think part of what's interesting is, as we
3 learn about the information that we've presented,
4 as we've heard different data about, for instance,
5 drug utilization patterns, both in children and
6 adults over the last decade or so, what we can see
7 is that there are declines in prescribing. And
8 what we know is that there are many, many factors
9 at play.

10 It was an interesting discussion as we try
11 to see the impact of our actions as an agency on
12 overall public health goals, but today we are going
13 to ask you very specifically about the impact for
14 the future development of these products for
15 children.

16 Thank you again, and I look forward to the
17 discussion.

18 DR. BROWN: Thank you, Dr. Hertz.

19 We need to return to introductions for just
20 a second. Dr. Draker?

21 DR. DRAKER: Bob Draker, a member of the
22 PAC, pediatrics, hematology, and blood bank

1 transfusion medicine, Syracuse, New York.

2 DR. BROWN: Welcome. And Dr. Linda Tyler is
3 on the phone.

4 DR. TYLER: I'm Linda Tyler, chief pharmacy
5 officer of [inaudible].

6 **Clarifying Questions**

7 DR. BROWN: Thank you, Linda.

8 Are there any clarifying questions for the
9 FDA from our discussions yesterday? Certainly, our
10 speakers from yesterday are not here, and we want
11 to try to focus our attention on -- if there are
12 any points of interest or clarifications that need
13 to be gotten from the FDA speakers or Dr. Hertz,
14 we'll take those at this time.

15 Dr. Patrick?

16 DR. PATRICK: Stephen Patrick from
17 Vanderbilt. Just a quick clarification. Are we at
18 all discussing pregnant women and their needs, or
19 is that a separate discussion?

20 DR. HERTZ: We would consider that a
21 separate area. We haven't really presented any of
22 that background.

1 DR. BROWN: Any other questions before we
2 move on to the open public hearing?

3 (No response.)

4 **Open Public Hearing**

5 DR. BROWN: Hearing none, both the Food and
6 Drug Administration and the public believe in a
7 transparent process for information-gathering and
8 decision-making. To ensure such transparency at
9 the open public hearing session of the advisory
10 committee meeting, the FDA believes that it is
11 important to understand the context of an
12 individual's presentation.

13 For this reason, the FDA encourages you, the
14 open public hearing speaker, at the beginning of
15 your written or oral statement, to advise the
16 committee of any financial relationship that you
17 may have with any industry group, its products, and
18 if known, its direct competitors. For example,
19 this financial information may include industry's
20 payment of your travel, lodging, or other expenses
21 in connection with your attendance at the meeting.

22 Likewise, the FDA encourages you, at the

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

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

20 Will speaker number 1 step up to the podium
21 and introduce yourself?

22 DR. MALVIYA: Good morning. My name is

1 Shobha Malviya, and I am here as the president of
2 the Society for Pediatric Anesthesia. And I'm also
3 representing the American Society of
4 Anesthesiologists, the Society for Pediatric Pain
5 Medicine, and the American Society of Regional
6 Anesthesia and Pain Medicine. In starting, I'd
7 like to state that I have no financial
8 relationships that are relevant to the content of
9 my presentation today, nor my presence here at the
10 FDA meeting today.

11 I am a pediatric anesthesiologist practicing
12 at the University of Michigan, and more
13 specifically, I provide care to children who
14 require congenital cardiac surgery, other general
15 surgical procedures, as well as those who need
16 perioperative pain management.

17 Our collective organizations appreciate the
18 opportunity to comment here today, and we applaud
19 the efforts of the FDA to discuss plans for
20 establishing safety and efficacy in the use of
21 opioids in children.

22 Prescription opioid abuse has impacted the

1 lives of many people across the United States, and
2 has now become widely known as a public health
3 crisis. What is less well known, however, is the
4 importance of treating pain and the far-reaching
5 consequences of poorly treated or inadequately
6 treated pain. This is particularly true relating
7 to the use of opioids in children.

8 Our organizations caution the FDA to take a
9 balanced approach, one that supports efforts to
10 reduce opioid overdose and misuse, but also
11 preserve the patient access to pain management
12 therapies.

13 Similar to adults, children also experience
14 moderate to severe acute and chronic pain that
15 requires adequate treatment. It is therefore
16 important that efforts to curtail opioid abuse,
17 misuse, or overprescribing do not inhibit
18 children's access to appropriate treatments.

19 Some children experience pain associated
20 with progressive underlying conditions, and others
21 suffer from severe pain stemming from conditions
22 such as cancer, sickle cell disease, and

1 musculoskeletal conditions that are refractory to
2 treatment. These facts highlight the need for the
3 availability of opioids, including
4 immediate-release, extended-release, and
5 long-acting opioid analgesics for the treatment of
6 both acute and chronic pain in children.

7 To ensure that pediatric patients continue
8 to have access to opioids, we support reasonable
9 regulatory approaches that incentivize prescribers
10 to obtain the proper education and training needed
11 to treat acute pain in children. Prescribers that
12 do not specialize in pain management should
13 consider consulting with pain medicine specialists
14 and refer patients with chronic complex pain
15 conditions.

16 Yet, with the limited availability of pain
17 management specialists in many regions of the
18 United States, this might require exploring
19 alternatives, such as web-based collaborations
20 between patients, providers, and specialists.

21 Our organizations also strongly support the
22 use of multimodal and multidisciplinary pain

1 management strategies, which may decrease reliance
2 on opioids. To this end, studies are urgently
3 needed that evaluate the safety and efficacy of
4 multimodal therapies, and these would include
5 non-opioid analgesics, as well as non-pharmacologic
6 measures.

7 Studies are also needed that identify
8 barriers to the routine use of these measures, and
9 such barriers would include inadequate insurance
10 coverage and high cost sharing requirements.

11 Furthermore, there is still a need for the
12 development of alternative medications for use in
13 the treatment of pain. For example, liquid
14 formulations of non-opioid analgesics, which are
15 already being used outside of the United States,
16 may be especially useful in the treatment of pain
17 in the U.S. pediatric population.

18 Sponsors seeking pediatric labeling should
19 be encouraged to develop and test formulations that
20 are appropriate and safe for use in children.
21 Additionally, post-marketing assessment of existing
22 and new analgesic drugs that have not yet been

1 approved for use in children would greatly
2 facilitate informed decisions regarding appropriate
3 dosing of opioid and non-opioid analgesics in
4 children.

5 Importantly, in addition to provider
6 education, the education of parents and families as
7 caregivers is essential to ensure the safe use and
8 disposal of not only opioids, but all medications
9 used in children. The home is the source of a
10 large proportion of opioid medications associated
11 with morbidity and mortality in children, who
12 either intentionally or unintentionally misuse
13 these medications. We encourage the FDA to partner
14 in the development of educational materials for
15 patients and families.

16 In closing, our organizations appreciate the
17 opportunity to weigh in on this important topic,
18 and I thank you for your time today.

19 DR. BROWN: Thank you very much,
20 Dr. Malviya. We appreciate your comments and your
21 representing the ASRA, the ASA, the SPA, and the
22 SPPM in these deliberations today.

1 Could speaker number 2 step to the podium
2 and identify yourself?

3 MR. THOMPSON: Good morning to all of you.
4 My name is Edwin Thompson. I'm the president of
5 Pharmaceutical Manufacturing Research Services,
6 located in Horsham, Pennsylvania, a professional
7 with 43 years' experience in the pharmaceutical
8 industry.

9 FDA committees have been convened to
10 consider the development of opioid analgesics for
11 pediatric patients. Specifically, you will be
12 considering appropriate pediatric populations for
13 the study of extended-release opioid analgesics.

14 I am here today unequivocally to state that
15 pediatric studies should never be conducted using
16 extended-release opioid analgesics. The reasons
17 are clear, clear. In the briefing document,
18 Dr. Nelson informed you the ethical principle
19 scientific necessity holds that children should not
20 be enrolled in a clinical investigation unless it
21 is necessary to achieve an important scientific or
22 public health objective concerning the health and

1 the welfare of children. Our corollary is that
2 children should not be enrolled in studies that are
3 duplicative or unlikely to yield important
4 knowledge applicable to children about the product
5 or the conditions under investigation.

6 The director of the Centers for Disease
7 Control and Prevention, Dr. Thomas Frieden, wrote
8 in a New England Journal of Medicine in April of
9 this year, "It has become increasingly clear that
10 opioids carry substantial risk and uncertain
11 benefits, especially as compared with other
12 treatments, for chronic pain."

13 So what scientific or public health
14 objective is so important and so necessary to the
15 health and the welfare of children that you would
16 exposure children to drugs that carry substantial
17 risk and uncertain benefits?

18 There is no scientific or public health
19 objective that warrants exposing children to drugs
20 with substantial risk and uncertain benefits. In
21 fact, it is highly unlikely that these studies will
22 yield important knowledge concerning the health and

1 the welfare of children.

2 In your briefing document, you were informed
3 by the FDA Office of Surveillance and Epidemiology
4 that in the United States outpatient retail
5 setting, there was a 34 percent decrease in the
6 number of pediatric patients who received
7 prescriptions for opioid analgesics from 2011 to
8 2015.

9 Annually, within each respective pediatric
10 age group examined, approximately 98.5 percent or
11 more of patients in each pediatric age group
12 received immediate-release analgesic prescriptions,
13 and 1.6 percent or less of patients in each
14 pediatric age group received extended-release or
15 long-acting analgesics throughout the study period.

16 Physicians are declining to use opioids not
17 because they're missing important information, but
18 because they know of the substantial risk and
19 uncertain benefits. There is no scientific
20 necessity here. The extended-release opioids in
21 particular fail the scientific necessity test.

22 The Code of Federal Regulations, 21 CFR 56,

1 requires that the selection of subjects must be
2 equitable. Equitable selection requires that
3 subjects who are capable of informed consent, for
4 example competent adults, should be enrolled prior
5 to subjects who cannot consent, for example
6 children. Data in adults is required in support of
7 the judgment that the risks of introducing the
8 intervention in children are justified by the
9 prospect of direct benefit; 21 CFR, that's 50.52.

10 Again, quoting Dr. Frieden, "More research
11 is needed to fill in critical evidence gaps
12 regarding the effectiveness, safety, and economic
13 efficiency of long-term opioid therapy."

14 You are required to conduct this research in
15 adults before you conduct research in children. At
16 this time, the prospect for a direct benefit to
17 children does not exist. The criteria for
18 initiating a clinical trial in children under the
19 higher risk pathway is that sufficient proof of
20 concept for a prospect of direct benefit exists
21 that justifies exposing children to the known, and
22 perhaps unknown theoretical risk of the

1 intervention.

2 The benefit of using opioids in the
3 treatment of chronic pain is transient, unproven,
4 and uncertain. The uncertain benefits prevent
5 exposing children to the known substantial risk of
6 opioid drugs in the treatment of chronic pain.

7 Next, there is no substantial evidence of
8 efficacy for opioids in chronic treatment of pain.
9 Scientific necessity requires that you have
10 efficacy in adults that a direct benefit exists
11 before considering exposing children to the known
12 risk.

13 Quoting Dr. Nelson again, "There is general
14 consensus that a child's exposure to risk in
15 pediatric research must be low in the absence of
16 direct therapeutic benefit to that child." In the
17 case of opioids used in the treatment of chronic
18 pain, there is an absence of direct benefit, and
19 the risk is potentially dangerous.

20 In addressing the risk of using opioids for
21 chronic pain treatment, Dr. Frieden wrote recently
22 in the New England Journal of Medicine, "We know of

1 no other medication routinely used for a non-fatal
2 condition that kills patients so frequently."
3 Thus, both the absence of substantial evidence of
4 efficacy and the morbidity and mortality resulting
5 from using opioids in the chronic treatment of pain
6 demands that you not conduct studies in children
7 for the treatment of chronic pain, and that you
8 remove the existing pediatric labeling for
9 OxyContin.

10 I want to clearly address the lack of
11 substantial evidence of efficacy with opioids in
12 chronic pain treatment, and specifically
13 extended-release opioids since they are approved
14 only for chronic treatment.

15 The Centers for Disease Control published
16 the CDC guidelines for prescribing opioids in
17 chronic pain on March 15, 2016, this year. In it,
18 the CDC makes 12 recommendations for stopping the
19 opioid epidemic and saving lives. And I wish to
20 remind you that there should be nothing more
21 important for the FDA and your committees than
22 stopping this opioid epidemic and saving lives.

1 Dr. Frieden has specifically stated, "The
2 guidelines use the best available scientific data
3 to provide information and recommendations to
4 support patients and clinicians in balancing the
5 risk of addiction and overdose with the limited
6 evidence of benefits of opioids for the treatment
7 of chronic pain." Surely you must heed these
8 critical recommendations.

9 Eleven of the 12 CDC recommendations are not
10 in the labeling for opioid products approved to
11 treat chronic pain, nor are they in the FDA REMS
12 program for informing and educating clinicians on
13 the best available scientific data and
14 recommendations for using opioids in the chronic
15 treatment of pain.

16 This is shocking. Six months later, and
17 15,000 deaths, without actions on the CDC
18 recommendations, and you want to meet today to
19 expand the use of opioids for pediatric labeling.
20 How can you get it so wrong?

21 Recently, the FDA added increased safety
22 warnings concerning the concomitant use of

1 benzodiazepine drugs and opioids to opioid
2 labeling. That recommendation was number 11 of 12.
3 The FDA should expeditiously also add the first 10
4 recommendations to the labeling.

5 I wish to remind you that there is currently
6 an iatrogenic opioid epidemic in the United States.
7 And in 2014 more than 28,000 persons died from an
8 opioid overdose that is largely due to prescription
9 drugs that were approved by the United States Food
10 and Drug Administration. Each and every day, the
11 number continues to grow.

12 If we go back to where the opioid epidemic
13 started, it will be clearly obvious on how to stop
14 this tragedy. In December 1995 the FDA approved
15 the extended-release opioid OxyContin for the acute
16 treatment of moderate to severe pain. I am showing
17 you the slides that were generated by this FDA
18 division in November of 2008. The label states,
19 "For the management of moderate to severe pain,
20 where use of an opioid analgesic is appropriate,
21 for more than a few days." Acute treatment

22 At the same time, the FDA labeled OxyContin

1 for abuse deterrents saying, quote, "The late
2 absorption as provided by OxyContin tablets is
3 believed to reduce the abuse liability of a drug."
4 Approving an extended-release drug for acute pain
5 treatment violates all scientific and medical
6 principles. For acute pain treatment, you would
7 use the lowest effective dose for the shortest
8 period of time. You would not choose an
9 extended-release opioid drug.

10 So why did the FDA approve OxyContin for the
11 treatment of acute pain, and on the unsupported
12 belief that it had abuse deterrent properties? It
13 is obvious that there is not substantial evidence
14 for efficacy in chronic treatment of pain, and
15 there is no evidence for abuse deterrence.

16 You have a drug that cannot be used for
17 acute treatment of pain, does not have efficacy in
18 chronic treatment, and is labeled uniquely safe due
19 to abuse deterrent properties that do not exist.
20 Physicians are being told that a drug is effective,
21 but when patients do not get results, the
22 physicians increase the dose.

1 Of course we have an opioid epidemic. This
2 mistaken belief also led to the approval of an
3 80-milligram and 160-milligram tablet and
4 accelerated the opioid epidemic. Both products are
5 over 200-morphine milligram equivalence per day, a
6 dose that produces death in 1 in 32 patients.

7 In 2000, there was widespread media and
8 state reports of OxyContin abuse and diversion,
9 which contributed to the 160-milligram version
10 being withdrawn from the market. In August 2001,
11 the FDA deleted the language regarding reduced
12 liability with CR formulation. Also in 2001, the
13 FDA changed the labeling from acute to chronic
14 treatment without substantial evidence of efficacy
15 in chronic treatment of pain.

16 If you have any doubt concerning substantial
17 evidence of efficacy, let me again quote
18 Dr. Frieden. "The few randomized trials to
19 evaluate opioid efficacy for longer than six weeks
20 had consistently poor results." There is no
21 evidence that opioids are efficacious for the
22 chronic treatment of pain. None.

1 You must not add pediatric labeling to
2 extended-release opioids, and you should remove the
3 pediatric labeling from OxyContin. You must have
4 documented evidence of effectiveness before you
5 approve and label a drug, and certainly before you
6 expand the label to children. The director of the
7 CDC has informed that you do not have documented
8 substantial evidence for using opioids in the
9 treatment of chronic pain.

10 Again to quote Dr. Frieden, "Efforts to
11 improve treatment of pain failed to adequately take
12 into account opioids' addictiveness, low
13 therapeutic ratio, and lack of documented
14 effectiveness in the treatment of chronic pain."

15 The FDA has not told you that they have
16 documented evidence of treatment in chronic pain.
17 Instead, the FDA is transferring responsibility and
18 liability for this expanded labeling to your
19 committees. In the absence of substantial
20 evidence, they are using your recommendation as the
21 evidence for this action. You must reject the
22 current and all additional opioid labeling for

1 treatment of chronic pain, including conducting
2 studies in children.

3 I urge the individuals in these committees
4 to utilize its advisory function to the fullest
5 extent possible. Take the appropriate steps to
6 combat the opioid epidemic, to remove the pediatric
7 labeling from OxyContin, and to not conduct
8 pediatric studies using extended-release opioids.

9 Dr. Frieden summarizes this subject by
10 stating, "The science of opioids for chronic pain
11 is clear. For the vast majority of patients, the
12 unknown, serious, and too often fatal risk far
13 outweigh, far outweigh the unproven and transient
14 benefits." Thank you.

15 DR. BROWN: Thank you, Mr. Thompson.

16 I'll remind the committee that consideration
17 of conflict of interest must be considered in
18 evaluating every speaker. Let us go on to speaker
19 number 3, if you could step to the podium and
20 identify yourself.

21 MS. BALDRIDGE: Good morning. My name is
22 Stacy Baldrige. I'm a nurse by training and a

1 clinical scientist with Purdue Pharma. I would
2 like to thank the advisory committee for the
3 opportunity to speak today as we work together
4 toward the common goal of providing important data
5 to healthcare professionals who care for pediatric
6 patients with pain.

7 Purdue has extensive experience with chronic
8 pain and conducting studies for chronic pain
9 treatment in pediatric patients. In working on
10 these studies, we have learned a lot about the
11 pediatric pain population and about study design
12 choices that impact the feasibility and
13 generalizability of pediatric clinical trials for
14 pain.

15 Pediatric epidemiology studies provide an
16 informative background to facilitate clinical
17 research. In order to better understand the
18 characteristics of pediatric patients with pain
19 severe enough to require opioids, as well as the
20 usual approach to treating these patients in
21 clinical practice, we conducted a series of
22 epidemiology studies. These studies are based on

1 data from healthcare claims databases and
2 electronic medical records.

3 While there are limitations in these data
4 sources, they reflect real-world usage patterns,
5 and the population is much larger and more
6 representative of actual clinical practice than a
7 clinical trial. Today, we are sharing data from
8 the largest of our epidemiology studies. The
9 objective of this study was to describe the
10 prevalence of conditions associated with pain in
11 pediatric patients and how these conditions are
12 treated.

13 The prevalence of conditions causing pain is
14 presented here, grouped by age, with the oldest age
15 group in green. Overall among commercially insured
16 patients, surgery was the most common pain related
17 diagnosis, followed by orthopedic conditions,
18 malignancies, trauma, and genetic conditions. As
19 you can see, most conditions have an increasing
20 prevalence with increased age.

21 The types of pain treatments used in these
22 patients vary substantially by condition and the

1 age of the patient, with older children receiving
2 treatment more frequently than younger children.
3 The use of immediate-release opioids was relatively
4 common, while the use of extended-release opioids
5 was notably rare.

6 An understanding of typical clinical
7 treatment duration may also inform trial design.
8 We want our trials to be generalizable to the
9 population of pediatric patients who receive
10 opioids in clinical practice. While most pediatric
11 opioid trials require opioids to be used for at
12 least 14 days, epidemiology data on treatment
13 patterns in clinical practice suggest that
14 prescriptions for opioids in pediatric patients are
15 generally of short duration.

16 The median treatment duration for
17 extended-release opioids was only 11 days, and
18 6 days for immediate-release opioids. Because of
19 this, identifying patients who meet trial duration
20 requirements may prove difficult. We should
21 consider if treatment durations of less than two
22 weeks is appropriate and sufficient to evaluate

1 safety.

2 The findings from our epidemiology studies
3 contribute to an understanding of the pediatric
4 pain population, which helps to inform the design
5 of future trials to improve their feasibility and
6 generalizability, while still providing sufficient
7 data to evaluate safety.

8 Most children with pain serious enough to
9 require opioids are older. Recruitment of patients
10 in the younger age group is often challenging, and
11 the comparative rarity of these patients, as seen
12 in our epidemiology studies, provides context for
13 why. A large proportion of pediatric patients with
14 pain have acute pain from surgery or injury.
15 Chronic pain in pediatric patients is comparatively
16 rare, and mostly in children with serious
17 underlying conditions, like cancer.

18 Finally, the real-world utilization patterns
19 do not mimic those specified in common trial
20 designs with respect to duration requirements.
21 This has major impacts on both the feasibility and
22 generalizability of pediatric clinical trial

1 results.

2 I will now shift gears to speak about
3 Purdue's pediatric clinical trial experience. We
4 conducted two pediatric clinical trials evaluating
5 opioids for moderate to severe persistent pain. We
6 collected prescreening information based on
7 investigator assessments of children considered for
8 study enrollment. For the OxyContin study, over
9 2,000 patients were prescreened to enroll 155
10 patients in the trial. For the Butrans study, over
11 3,000 patients were prescreened to enroll 41
12 patients.

13 For the OxyContin study you can see the
14 distribution of ages presented here, with
15 prescreened patients in blue and enrolled in red.
16 The overwhelming majority of patients prescreened
17 and enrolled were in the older age group, similar
18 to the pattern seen in the epidemiology data. A
19 summary of medical conditions of prescreened and
20 enrolled patients is presented here, with pain
21 related to surgery, malignancy, and traumatic
22 injury as the most common.

1 The most frequently reported reason for not
2 participating in the trial was the failure to meet
3 inclusion criteria related to treatment. This
4 included both the minimum dose requirement and the
5 expected duration of use. This exclusion was cited
6 for approximately 40 percent of those who were
7 prescreened but not enrolled. Other common reasons
8 for not participating were the age requirement and
9 opioid tolerance requirements.

10 The Butrans prescreening database reinforces
11 that the majority of patients prescreened and
12 enrolled are in the adolescent age group. In this
13 study, the most common conditions for prescreened
14 patients were pain related to surgery, acute pain,
15 sickle cell disease, and malignancy.

16 Patients in this study were excluded
17 primarily due to the age requirement, expected
18 duration of treatment, or use of protocol-specified
19 prohibited medications, like diphenhydramine and
20 ondansetron. The high numbers of required
21 prescreened patients to reach enrollment goals
22 reinforced the difficulty of conducting clinical

1 trials for pain in pediatric patients, and the need
2 for careful consideration of study criteria.

3 In addition to the learnings from our
4 epidemiology studies and our trial prescreening
5 data, we've learned a lot in the course of
6 executing these studies. Clinical trial
7 feasibility is influenced by patient
8 characteristics and trial eligibility criteria, but
9 also impacted by operational factors related to
10 unique patient populations and investigator
11 selection.

12 One example of a unique patient population
13 is in pediatric oncology patients. The FDA has
14 requested that children with cancer related pain be
15 included in pediatric pain studies. These patients
16 have specific challenges that may prohibit their
17 inclusion in such trials. In support of inclusion
18 of these patients, we recruit pediatric oncologists
19 as investigators and sub-investigators, and we ask
20 our study teams to consider oncology patients in
21 their recruitment efforts.

22 Children with cancer related pain are

1 frequently on oncology-specific trials or treatment
2 protocols that prohibit trial participation for
3 symptom management. With complex medical
4 conditions, and multiple concomitant medications,
5 including many that are excluded by protocols,
6 these children are frequently ineligible for trials
7 of opioids, impacting the feasibility of their
8 enrollment.

9 A final feasibility issue is related to site
10 and investigator recruitment. The selection of
11 investigators and institutions should reflect those
12 with expertise in pediatric pain management and
13 research to contribute to the safe conduct of
14 trials and collection of quality data. With an
15 increasing number of pediatric analgesic trials,
16 investigators and sites with sufficient resources
17 and patients to conduct such studies are in great
18 demand. In our experience, investigators who are
19 part of large children's hospitals or academic
20 institutions with multidisciplinary pain services
21 are well suited to conduct the trials.

22 There are challenges in site recruitment as

1 many institutions are conducting multiple analgesic
2 studies that compete for both resources and
3 patients. This in turn has an impact on
4 willingness to take on new studies, study conduct,
5 and enrollment of patients in a reasonable amount
6 of time.

7 Finally, researchers at Purdue, like me, are
8 committed to evaluating the safety of opioids in
9 the pediatric population, as well as conducting
10 pediatric clinical trials that are feasible and
11 generalizable. Remember, we are working with a
12 rare population of pediatric patients with
13 persistent pain.

14 Clinical trial design should align with
15 medical practice as much as possible to maximize
16 the feasibility of completing these important
17 safety studies quickly, as well as their
18 generalizability to the population of pediatric
19 patients with pain in order to help manage this
20 rare and special population. Thank you.

21 DR. BROWN: Speaker number 4, if you could
22 step to the mic and identify yourself, please.

1 DR. HOUCK: Thank you. My name is
2 Dr. Connie Houck, and I am a pediatric
3 anesthesiologist from Boston Children's Hospital,
4 and chair of the American Academy of Pediatric
5 Surgical Advisory Panel, which is made up of
6 leaders of all of the pediatric surgical specialist
7 sections within the academy, including
8 anesthesiology, general surgery, neurosurgery,
9 ophthalmology, orthopedic surgery, otolaryngology,
10 plastic surgery, radiology, urology, and oral
11 health, which is the dentists. I have no financial
12 disclosures.

13 Pediatric surgical specialists are on the
14 front lines of the treatment of acute and
15 post-operative pain in children. We are
16 increasingly concerned that there is inadequate
17 information to inform our care of post-operative
18 pain, and insufficient safeguards to prevent our
19 patients from both overtreatment and undertreatment
20 of pain.

21 Recently, we've been asked by an increasing
22 number of parents of children and adolescents not

1 to provide opioid treatment for post-operative pain
2 due to concerns regarding addiction. There's an
3 urgent need for education and study informed
4 labeling of analgesics for children and adolescents
5 in the perioperative period.

6 Advances in pediatric surgery in the last
7 50 years have made it possible to repair many of
8 the congenital defects in infants and children that
9 were lethal in years past. It has also increased
10 the need for safe and effective medications for the
11 treatment of perioperative pain, and rational
12 strategies to reduce side effects.

13 The lack of pharmacokinetic and
14 pharmacodynamics studies of opioids in infants and
15 children has made the treatment of post-operative
16 pain problematic and potentially unsafe. Studies
17 since the 1980s have also shown that undertreatment
18 of pain in neonates and infants can have
19 detrimental, long-term physical and psychological
20 effects, which puts our patients at even further
21 risk.

22 There is no evidence that providing

1 appropriate labeling of opioids in children
2 increases use. In fact a recent research letter in
3 JAMA Pediatrics suggested there was actually a
4 decrease in the already very low number of
5 prescriptions for OxyContin written for children 11
6 to 17 years of age in the years since the labeling
7 changes were made in 2015.

8 As pediatric surgical specialists and
9 dentists, we recommend the following. Number one.
10 Robust studies of all opioid analgesic agents in
11 order to provide appropriate labeling of opioid
12 medications for use in infants, children, and
13 adolescents in the perioperative period. Without
14 specific studies in children, we risk both
15 overtreatment and undertreatment of pain in
16 children, and long-term consequences of these
17 ill-informed prescribing decisions.

18 Number two. Balanced regulatory approaches
19 that motivate prescribers to obtain the proper
20 education and training to appropriately treat acute
21 pain in children. This education must include
22 specific strategies that have been shown to be safe

1 and effective in infants, children, and
2 adolescents, for both inpatient and outpatient
3 surgery, including multimodal approaches for
4 perioperative pain control.

5 Number three. Specific guidance as to the
6 appropriate techniques for disposal of unused
7 opioid analgesics. Recent studies have shown that
8 for many pediatric surgeries, there may be extra
9 pain medicine that is not needed and is stored by
10 caregivers for further use. Surgical specialists
11 and dentists need to know how to counsel parents
12 about both the appropriate use and the disposal of
13 opioid medication that is not needed.

14 As the surgeon general, Vivek Murthy, has
15 recently stated in his letter to all physicians in
16 the U.S., "We must educate ourselves to treat pain
17 safely and effectively," and I quote. This is
18 difficult for pediatric surgical specialists and
19 dentists to do when there is limited information
20 about the pharmacokinetics and pharmacodynamics of
21 analgesic agents in children, and these most recent
22 guidelines from the CDC that Dr. Murthy has

1 suggested that all physicians read, does not
2 include any specific information for children less
3 than 18 years of age.

4 Pediatric surgical specialists and dentists
5 need up-to-date information about the safe and
6 effective use and disposal of opioids in children
7 and adolescents in order to provide optimal
8 perioperative care to our patients and families.
9 The best way that we can protect children is to
10 increase our knowledge about the use of analgesics
11 in children, not increase their suffering by
12 avoiding effective treatments due to ignorance or
13 fear.

14 DR. BROWN: Thank you, Dr. Houck.

15 There was another speaker but apparently
16 there's not. The open public hearing portion of
17 this meeting has now concluded, and we will no
18 longer take comments from the audience. The
19 committee will now turn its attention to address
20 the task at hand, the careful consideration of the
21 data before the committee, as well as the public
22 comments that we have heard.

1 I'm going to ask -- Dr. Sharon Hertz will
2 now provide a charge to the committee.

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

4 DR. HERTZ: I don't have a lot more to say
5 from this morning. We have a lot of questions, and
6 as you go through these questions, I would like to
7 underscore how much, not just direct answers, but
8 the rationale for the answers are really heavily
9 weighed and considered by us when we take back the
10 advice given from an advisory committee setting.

11 You might notice, we don't have voting
12 questions here because what we're really trying to
13 do is figure out the best way to fulfill our
14 mandate to study medications in children, and in
15 this case today, opioid analgesics. So rather than
16 read the full page of questions, they will be read
17 prior to each discussion, they'll be read into the
18 record. So I just will turn it back over to
19 Dr. Brown so we can begin.

20 **Questions to the Committee and Discussion**

21 DR. BROWN: Thank you, Dr. Hertz. We will
22 now proceed with the questions to the committee and

1 the panel discussions. I would like to remind any
2 of our public observers that while this meeting is
3 open for public observation, public attendees may
4 not participate except at the specific request of
5 the panel.

6 I'll now read the first question for
7 discussion. Let me say before we get started, the
8 expectation of the Food and Drug Administration for
9 this committee is that there will be a robust
10 discussion of each and every one of these
11 questions. We want everyone on the panel to be
12 involved, voting members, non-voting members.
13 Please keep that in mind.

14 Question number 1 for discussion. Discuss
15 safety concerns associated with the use and study
16 of opioids in pediatric patients and whether
17 patient selection or management of these risks
18 should differ from adults. Include in the
19 discussion the safety of opioid analgesics in
20 pediatric patients in terms of adverse events, as
21 well as risks of misuse, abuse, addiction,
22 overdose, and death.

1 Is that question clear to the members of the
2 panel?

3 (No response.)

4 DR. BROWN: Response. Dr. Walco?

5 DR. WALCO: I think if we're talking about
6 the issue of safety, one element that was brought
7 up yesterday but not really highlighted is the
8 danger of untreated or poorly treated pain in
9 children. And the studies would indicate that
10 especially at certain vulnerable ages, when
11 children are young and nervous systems and pain
12 systems are developing rapidly, poorly treated pain
13 may have lasting, profound, and irreversible
14 effects, sensitizing them to greater risk of
15 difficulties with pain in the future.

16 If the question is, are we looking at risk
17 differently in children versus adolescents, I would
18 encourage us to not just look at the risk of the
19 medications that we're talking about, but also the
20 risk of not using the medications and leaving pain
21 poorly treated.

22 DR. BROWN: Dr. Walco, I'm going to ask you

1 if you could expand on that. We've heard that. Is
2 there any way that we can quantify that that would
3 inform the discussion?

4 DR. WALCO: I think, not surprisingly, the
5 theme of inadequate data will rear its ugly head
6 here again. The animal data -- largely produced by
7 the groups in London, Maria Fitzgerald started the
8 work back in the '80s, and is being continued by a
9 number of others on animals -- show that if you
10 insult an area of the body as the nervous system is
11 developing, there's an overgrowth of nerves, and
12 you lose the integration. So what that basically
13 means is that pain is exaggerated and it's diffused
14 rather than focal.

15 In addition, there are data to indicate that
16 there are changes that go on in the central nervous
17 system such that there's increased central
18 sensitization of pain responses, especially if the
19 insults are repeated. So what that would mean is
20 that any nociceptive stimulus coming in would be
21 perceived as significantly more painful for
22 physiological reasons not psychological reasons

1 alone.

2 Follow-up data of premature infants show
3 that some of the insults that are received during
4 their treatment early on have lasting effects,
5 certainly through early childhood. And as these
6 cohorts are followed, such as by Dr. Grunnau in
7 Vancouver, she's still finding sequelae even as
8 children hit the adolescent years.

9 The other angle one could take is if you
10 look at the IMPACT panel that was done looking at
11 the relationship between the development, or the
12 quote/unquote, "transition of chronic pain in
13 adults," we know that poorly treated perioperative
14 pain puts people at greater risk for chronic pain
15 down the line. There are not necessarily clear
16 data in pediatrics, but certainly there's no reason
17 to assume that would not be the case.

18 It's an area where there's a growing body of
19 literature, and clearly the idea that poorly
20 treated pain is a major risk factor is something
21 that one needs to consider.

22 DR. BROWN: I know in discussions with

1 Dr. Yaksh at UCSD, he has said many of the things
2 that you're saying today, and lamented the fact
3 that there is not much interest at the National
4 Institutes of Health to support research in that
5 regard. So one recommendation might be that we
6 have some interaction at that point.

7 DR. WALCO: I alluded to it yesterday. I
8 think the tragedy is that -- you've heard about the
9 CDC guidelines. In the second paragraph of those
10 guidelines it states outright that anybody under
11 18, the guidelines do not pertain to them. And I
12 think there's some profound risk of extrapolating
13 or generalizing those recommendations to children
14 without really understanding the issues.

15 Similarly, the National Pain Strategy was released
16 through HHS in March, and children were completely
17 neglected from that.

18 The good news is that there will be a
19 national pain research agenda that's being
20 generated through HHS, and there was a systematic
21 effort to include pediatric people in each of those
22 working groups, especially focusing on chronic

1 pain. So some of the issues that we're talking
2 about hopefully will be better addressed, and
3 pediatrics will be included.

4 DR. BROWN: Thank you, sir. Dr. Turer?

5 DR. TURER: So this is not my area of
6 expertise.

7 DR. BROWN: If you could just --

8 DR. TURER: Oh, yes, Christy Turer, UT
9 Southwestern. Although pain is not my area of
10 expertise, as an internist, I will say, and I think
11 that this area is under studied, to echo Dr. Walco,
12 I've had patients who have PICC lines placed or
13 ports placed because they had pediatric conditions
14 and had multiple sticks, and are so fearful of
15 blood draws as adults.

16 So I think that this is an area that should
17 be studied. What is the impact longitudinally of
18 children who have these chronic illnesses, are
19 hospitalized for prolonged periods? Because it's
20 not just one or two patients. I've seen this time
21 and time again, and have number been able to find
22 any data on it. You know, putting in PICC lines,

1 these patients are at risk for secondary
2 infections, and we're constantly trying to talk
3 with them and get these things out, but they are
4 just so incredibly fearful of small needle sticks
5 as adults.

6 DR. BROWN: Dr. Ruha?

7 DR. RUHA: Michelle Ruha. Just regarding
8 some of the discussion points. So the patient
9 selection, how might it differ from adults, well
10 obviously with adults we can do studies, even in
11 people who maybe don't need opioids, we can do
12 pharmacokinetic studies. And obviously we would
13 never want to study healthy children, but we don't
14 want to withhold opioids from any children who need
15 them and who are in pain.

16 So I think it seems obvious that the
17 children that we should study are the children who
18 need and are on opioids because they're going to be
19 receiving them anyway.

20 But the part that I am more familiar with is
21 the adverse events, the misuse, abuse, as a medical
22 toxicologist addiction and overdose is what I see

1 all the time. And I feel that it's really
2 important to study the opioids in children with
3 pain so that we can better identify which opioids
4 are safe, understanding the pharmacokinetics.

5 I feel that since we're extrapolating from
6 adults, all opioids pretty much are used in
7 children. And obviously with some, like codeine,
8 we've learned that they are not safe. And I would
9 say that the use of methadone in a lot of
10 situations treating children in pain with methadone
11 is not safe either.

12 I feel like we really do need to study the
13 children who come in with acute painful conditions
14 and will be going to surgery, enroll them in
15 studies, not subject them to additional blood
16 draws, but identify those children to study
17 prospectively. And in addition to monitoring for
18 adverse events, doing pharmacokinetic studies as
19 possible.

20 Also do long-term follow-up to perhaps
21 compare risks later, risk of misuse perhaps in
22 children with immediate-release preparations versus

1 those who ultimately go on temporary use of long
2 acting. If we can get enough numbers, compare
3 risks of later misuse in those different
4 preparations also.

5 DR. BROWN: Dr. White?

6 DR. WHITE: Michael White, New Orleans.
7 Thank you. I started out with concerns about how
8 do we select which of the opiates we should look
9 at, because clearly the safety profile is different
10 for many of the opioids.

11 The CYP2D6 in particular affects codeine,
12 and dihydrocodeine I believe, in an adverse way
13 where you potentially could have lethal doses, or
14 at least exceptionally high doses using the same
15 dose as you might in other children. And that's a
16 fairly high proportion of some ethnic groups, and
17 we have no way to predict which of those might be
18 affected before giving the dose. We had a meeting
19 in December, and many of us at the table were also
20 part of that discussion.

21 So I think first we should select which
22 opioids we should be looking at. And part of that

1 selection process should be which of the opioids
2 have the best safety profile in adults, or the
3 greatest safety profile, and focus on those with
4 efficacy and safety first when we're designing our
5 trials.

6 Then the other place -- and this is very
7 scattered, but the other place we run into problems
8 is the idea of if you're in a trial, you should
9 only be in one trial at a time. It's not an
10 absolute.

11 One of the populations of patients that
12 would be potentially useful in studying drugs for
13 pain relief are the pediatric patients in
14 hematology and oncology trials. When you bring
15 those up, those children are already in a trial,
16 and then to add them to another trial sometimes
17 presents a barrier.

18 I know it will be difficult to get that
19 through many IRBs, but maybe that's something we
20 should look to see if we could do nested trials in
21 COG protocols, or other places where we could nest
22 within the protocol for the treatment studies of

1 opioids, and the results of that might be helpful
2 to us.

3 I know those are two totally different
4 related concepts, but for -- I don't really know
5 how to wrap that up. But I think we should decide
6 first what opioids are safest and most efficacious
7 in adults before we decide to do trials in
8 children, and approach those that are the safest
9 and most efficacious.

10 DR. BROWN: Dr. Patrick?

11 DR. PATRICK: Thank you. I wanted to bring
12 up, again, the special group of pre-term infants,
13 around 50,000 very low birth weight infants born
14 every year, and around 27,000 infants born with
15 neonatal abstinence syndrome. And essentially
16 every drug that we use is off-label, and there
17 really is a need. We use a ton of drugs like
18 fentanyl in the U.S. NICUs, and there's very little
19 safety data. And there's some data to suggest
20 potential long-term cognitive issues.

21 I realize, as a part of the discussion
22 yesterday, there's some substantial difficulty in

1 studying this population. But in part, as we think
2 about safety concerns moving forward, and I just
3 wonder if it's worth thinking through how do we
4 partner with other groups, such as the Neonatal
5 Network, or even the Vermont Oxford Network, that
6 collect data in many of our NICUs, at least to
7 begin to collect data on safety moving forward for
8 both of these populations.

9 DR. BROWN: Dr. Czaja?

10 DR. CZAJA: Angela Czaja. I just wanted to
11 make sure that when we think about safety concerns,
12 we've talked a lot about the potential unintended
13 consequences of misuse and abuse in addiction,
14 which I think we discussed yesterday, it can be a
15 pretty complex issue.

16 One thing I think we haven't spoken as much
17 about is the acute safety concerns from a pediatric
18 intensive care perspective, the respiratory
19 depression, the hemodynamic effects. And if we
20 don't have a good understanding of the differences
21 of PK/PD at various different ages, then we have a
22 little bit more trouble being able to determine

1 what those potential acute, potential
2 life-threatening effects are.

3 I guess it's just to keep in mind that
4 although I understand the issues that are being
5 brought forth and the concern about these longer
6 term effects, that there are some very acute issues
7 that I think become very relevant when we're trying
8 to know how the different medications may act in
9 the different stages of life and development.

10 DR. BROWN: Dr. Hoehn?

11 DR. HOEHN: Sarah Hoehn. This is in
12 follow-up to what Angela just said as well. But I
13 think we're using these drugs a lot in ICUs all
14 day, every day, high doses, low doses, fentanyl,
15 morphine. So I think we have to have some safety
16 data on what to do.

17 I think it would be nice if there was some
18 way people could coordinate some sort of a database
19 to the PLESI [ph] network or similar to people were
20 saying within the neonatal network. Because every
21 institution has their own protocols, their own
22 preferred drugs for who uses fentanyl, who uses

1 morphine for different things. But there's a lot
2 we don't know in terms of delirium, and people who
3 are maybe intubated for two weeks who end up on
4 methadone for six or eight weeks, versus people who
5 are intubated for two weeks who are then rapidly
6 tapered off within five days.

7 So I think there's a lot of variability in
8 ICU management that impacts sort of long term in
9 terms of who's on which drugs at home and how
10 quickly and slowly we're tapering.

11 So it would be nice if there was some way, I
12 would say, to study children who are already
13 receiving these drugs and looking at the whole
14 scope of the spectrum in terms of some of the side
15 effect Angela just mentioned in terms of which
16 drugs you start with, and then more advice in terms
17 of delirium, how do people wean, you know sort of
18 developing guidelines for both initiation, and then
19 for getting them off, so you don't have a bunch of
20 kids at home that are tapering on methadone for a
21 month from a two-week pneumonia intubation.

22 I don't know how to do that, but I think if

1 someone could coordinate that in the world, it
2 would be nice.

3 DR. BROWN: Dr. Gerhard?

4 DR. GERHARD: Toby Gerhard, Rutgers. I'm an
5 epidemiologist, not a clinician, so there are many
6 people much more qualified than me to speak about
7 some of the clinical issues. One thing kind of
8 from my perspective that I want to bring up for the
9 discussion, make sure that we don't overlook this,
10 is that I think when we talk -- like for example,
11 in question 1, but it goes through all these
12 questions, obviously the pediatric population is
13 incredibly diverse, and I think many of the
14 questions that we talk about, the individual safety
15 concern regarding acute safety issues like
16 respiratory depression, versus risk posed by
17 potential addiction, change dramatically over that
18 age span.

19 I think the acute safety concerns are much
20 more at the forefront when we talk about the
21 younger ages, infant population, and so on. And
22 the addiction risks become more prominent when we

1 talk about adolescents, particularly if we expand
2 that definition along with the kind of pediatrics
3 association and go into kind of college age even.

4 So I think we just need to be very mindful
5 of kind of focusing the discussion on specific
6 populations because I think the issues change
7 dramatically. With all of these, we have kind of
8 this I think somewhat side concern in this context
9 of diversion, which can happen at any age group.
10 And that's something that generally needs to be
11 controlled in any population.

12 But obviously kind of what the safety
13 information is that we need to generate through
14 these trials and many issues with enrollment change
15 dramatically across the age span. So I think
16 that's just something to be aware of and to be
17 concrete about when we have these discussions.

18 DR. BROWN: Dr. Cnaan?

19 DR. CNAAN: Avital Cnaan. First, I'm a
20 biostatistician not a clinician either. I wanted
21 to bring up a couple of these special populations
22 as well. The oncology patients, the sort of

1 prevailing approach in the academic centers is
2 indeed let's try to have every patient on a COG
3 study. That is the generic approach.

4 I think in order to conduct these studies,
5 there has to be a dialogue. It may or may not work
6 to enter answering these questions as sub-
7 objectives in the COG study, but what we can at
8 least do is dialogue whether these studies are
9 sometimes for certain groups of oncology patients,
10 where you actually have already standard treatments
11 and are trying something new, but the something new
12 might be in the pain department rather than in the
13 next oncology agent department.

14 So that's one thought to sort of add to make
15 this dialogue work a little better.

16 The other special group that was mentioned
17 yesterday but not today is the palliative group
18 that might be oncology but might be other
19 palliative. And they are a special group. And in
20 there, the safety considerations might be the right
21 dosing and side effects, but as Dr. Feudtner said
22 yesterday, the long-term addiction is not an issue.

1 So the thinking about those studies need to be a
2 little bit different.

3 As I think Dr. White said, this is going to
4 take not one study at a time, but probably several
5 concurrent studies on very differing populations
6 and needs and risks.

7 DR. BROWN: Dr. Neville?

8 DR. NEVILLE: I have a couple points. One
9 is, I don't have anything to disclose because we're
10 not doing any pain studies, but obviously I have an
11 interest in it. And we're not doing those studies
12 because I couldn't contribute or accrue in a
13 meaningful manner. And so oftentimes, to the
14 previous point made, is palliative care patients
15 and post-op patients are excluded. We could not
16 find a single patient in our institution on opiates
17 for two weeks.

18 I think when we're looking at selection of
19 these studies, in order to balance the safety and
20 study these children, I think some of the inclusion
21 criteria of current studies need to be modified to
22 include the very patients who need these drugs the

1 most.

2 The other point I wanted to make, and to
3 Dr. Patrick's point, I agree completely with
4 Dr. Yao having participated in some of the
5 pediatric trial network opportunistic studies that
6 they are very difficult to do. But these are some
7 drugs that I think warrant consideration for those
8 types of studies.

9 They're difficult, but they can be done.
10 They can be done in a pilot nature to give us some
11 initial PK/PD data. They can be done in a
12 widespread patient population, including pre-term
13 babies. And safety data can be collected in
14 patients that are already getting a wide variety of
15 drugs. And so we don't put patients at increased
16 risk because they're already getting the drug, it
17 just requires meticulous and coordinated efforts.
18 So I think that's something that should be
19 considered.

20 DR. BROWN: Dr. Jones?

21 DR. JONES: In looking at the discussion
22 question and just thinking about how trials might

1 be designed differently in kids than adults, I
2 think one thing related to safety is that kids are
3 a particularly vulnerable population for accidental
4 overdoses because kids get into medicine cabinets
5 and their siblings could get into the medicine
6 cabinet.

7 I think in safety trials, if not already
8 discussed to do so, you should make sure that part
9 of the safety outcomes includes making sure that
10 medicines are returned that aren't used at the end
11 of the study, or making sure that they're dispensed
12 appropriately. Because I think that's a different
13 potential risk in children than adults.

14 DR. BROWN: Dr. Wade?

15 DR. WADE: Thank you. Kelly Wade,
16 Children's Hospital, Philadelphia. I really just
17 want to echo what Dr. Neville has just said, that
18 this may be an area, given our essential need for
19 data, to guide our decision-making. And the use of
20 opiates in complicated pediatric patients in
21 children's hospitals, that one difference may be
22 that this area in pediatrics may be well suited to

1 an opportunistic design, that obviously these
2 opportunistic designs have challenges, but we're
3 doing better and getting better at prospective data
4 collection.

5 This opportunity would allow us -- the
6 opportunistic trial design would allow us to
7 collect very important information and data on
8 patients actually receiving opiates in the
9 inpatient setting for these severe, complicated
10 pediatric conditions that exist. But I think we
11 could use that opportunistic design to not only
12 look at safety information, but to also get
13 critical information on efficacy, and also on
14 opiate-sparing modalities that are currently in use
15 for these patients.

16 There's a variety of opiates used across
17 different sub-specialty disciplines and across
18 different children's hospitals, so spreading this
19 in a multi-center way would also allow us to
20 compare the use of different opiates, different
21 safety signals, and differences in opiate-sparing
22 modalities.

1 DR. BROWN: Thank you for that comment.
2 We're going to try to focus our attention on the
3 questions individually so that the agency can
4 derive as much information about specific
5 questions.

6 So for the purposes of discussing question
7 1, let's focus our attention on primarily safety
8 concerns. And that would include safety concerns
9 around the administration of opioids, but it would
10 also surround the issue of having children included
11 in research studies as well as deriving data on the
12 current state of safety for the opioids that are
13 being given to children today.

14 So can we back up and look at that in terms
15 of safety? Dr. McCann?

16 DR. MCCANN: Dr. McCann from Boston. I'll
17 try to put a safety spin on this. One thing that I
18 think that we have not discussed at all is the use
19 of narcotics for sedation. And we've had a number
20 of ICU doctors talk about weaning from ventilators,
21 et cetera. And I think especially in the youngest
22 patients, we don't know much about narcotics in

1 neonates or premature babies at all.

2 Having just recently gone to a lecture by
3 Dr. Maria Fitzgerald from London, she tells you
4 that she can't even define pain in the neonate.
5 And just like Dr. Walco said, that inadequately
6 treated pain changes brain pathways, possibly
7 forever, there are also changes that occur in these
8 neonates if they've been exposed to opioids.

9 I almost wish that we had a separate meeting
10 just devoted to infants less than 3 months of age,
11 because although life is a continuum, they are at
12 an extreme, and they're so different from say an
13 adolescent or a latency aged child, that I think
14 that it would be beneficial to really just discuss
15 them as a group, and to think about studies for
16 them. I just want to reiterate, I think we have
17 very, very little information on any domain you
18 look at when it comes to neonates.

19 DR. BROWN: Dr. Flick?

20 DR. FLICK: As I look at the question, the
21 question asks, as you said, Dr. Brown, about safety
22 concerns. But the safety concerns seem to be quite

1 different depending on the population. A lot of
2 people, including Dr. McCann just now, have talked
3 about different populations. So we have the
4 neonates, we have children in palliative care. It
5 really depends on the population and the setting;
6 is it inpatient, is it outpatient?

7 But the second part of the question refers
8 more specifically to misuse, abuse, addiction, and
9 overdose and death, which I think, at least in my
10 mind, focuses the discussion mostly on adolescents.
11 And I don't know if the rest of the group sees it
12 that way, but it seems to me that the population
13 and the setting that we should most focus on are
14 adolescents as outpatients.

15 DR. BROWN: I'm going to say that I think
16 that safety concerns -- I guess I'm going to side
17 with Dr. McCann and say that safety concerns can be
18 utilized as a general term. We have license here
19 to discuss safety in all groups. We have them as
20 data about adolescents. And from my take on this,
21 that's a big problem because we have the most data,
22 that data is not very good, and we have much less

1 data on the patients that Mary Ellen is talking
2 about. So I think that we should think in terms of
3 issues relating to all the data.

4 Gary Walco yesterday spoke about defining
5 the groups into smaller subsets I believe. So I
6 think we should be looking at all groups.

7 Dr. Kibbe?

8 DR. KIBBE: I don't have patients, but I did
9 notice the other day that presentation from our
10 gentlemen who did pediatric orthopedic, that they
11 use a lot of opioids. So they must have some level
12 of comfort in order to prescribe it for all their
13 patients, and 46 percent of them use hydrocodone.

14 I think first we're struggling with how do
15 we pay for getting new information. Retrospective
16 studies are cheaper than prospective studies
17 because you don't have to enroll any patients. You
18 already have them. You already have records. I
19 wonder what the gentlemen who responded to his
20 survey would say the reason they selected that drug
21 in that patient and how they linked the two
22 together.

1 Safety and efficacy are linked. The safety
2 concerns about overdose and death are in patients
3 that we're treating, as well as in individuals who
4 decide to do things that are outside what we're
5 treating or the therapy that we're trying to
6 accomplish.

7 Why do the physicians pick these drugs to
8 use in these patients? And it's relatively easy
9 mathematically and with a computer to set up a
10 matrix where you have the age, the diagnosis, using
11 whatever code diagnostic numbers you want, and then
12 the use of the drug and whatever outcomes they had,
13 and try to tease out what would be a safe and
14 effective dose in a range of patients.

15 One other thing there was a lot of
16 discussion about, we don't want to stick them. You
17 don't want to stick them. If you're just looking
18 for the half-life of the drug in that particular
19 patient, you can do that with urinary collections.
20 And that's not a difficult pharmacokinetic shift in
21 the way you do calculations.

22 The study design for a prospective study is

1 easier to control, and therefore you use less
2 people. But when you're looking, and you're trying
3 to mine data that's already existing for a trend in
4 use rates, and why that trend seems to be effective
5 and seems to be a comfort level for the physicians
6 that are prescribing it, you might find a lot of
7 information about at least the range of doses that
8 people think are reasonable to start with each
9 individual group from their own experiences with a
10 number of patients that they've treated.

11 You can't do better than that until you nail
12 down exactly the levels of drug that work in
13 pediatric patients of different ages. But it's a
14 good place to start, and we're struggling with
15 getting information. Everything that I hear around
16 the table is, I don't know, I don't know, I don't
17 know, but everybody around the table prescribes
18 opioids for pediatric patients, so we must know
19 something. And it's just not being collected and
20 codified and put into use.

21 So I recommend that. And if you want to
22 know how to calculate the rate constants for

1 elimination from urinary excretion data, I'd be
2 happy to show you how to do that.

3 DR. BROWN: Thank you, Dr. Kibbe.

4 Dr. Bateman?

5 DR. BATEMAN: I was struck yesterday during
6 Dr. Levy's presentation about just how little we
7 really know about the impact of opioid exposure
8 when prescribed for pain relief and the risk of
9 future opioid misuse. We heard some discussion
10 that childhood is a developmentally vulnerable
11 stage, and that the brain circuitry might be
12 predisposed to some of the priming associated with
13 exposure.

14 But only a single study was presented that
15 had real data on the risk of future misuse, and
16 that suggested about a 30 percent increase in the
17 risk. But the confidence intervals on that study
18 are very wide. It's only a single study. And we
19 really don't have any information on the impact of
20 duration, the age at exposure.

21 There are certainly clinical circumstances
22 where opioids are absolutely needed in pediatrics,

1 and we heard that from multiple presenters. But
2 there are situations where the risks and benefits
3 of the drugs need to be weighed. And without that
4 long-term data, I think it's a challenging calculus
5 to undertake.

6 So I would just say, I think this is an
7 important priority area for research funded by the
8 FDA, by NIH, to understand that link.

9 DR. BROWN: Dr. Higgins?

10 DR. HIGGINS: I concur totally. And I think
11 that Dr. Feudtner's presentation really got me
12 thinking about the real need for longitudinal data.
13 There's that tension between individual-level use,
14 and then perhaps later misuse at the societal
15 level. And I really think that there needs to be
16 significant investment in some longitudinal
17 research.

18 DR. BROWN: Dr. Havens?

19 DR. HAVENS: Thank you. Peter Havens. So I
20 appreciated Dr. Walco's statements about the later
21 potential for hypersensitivity and other problems
22 with inadequate analgesia. As I look at the

1 question, it seems to focus mostly on the side
2 effects of giving too much drug.

3 I want to make sure that we all remember the
4 work of Anand and Hickey when they showed that
5 inadequate analgesia during cardiac surgery in
6 neonates increases the risk of death. So
7 inadequate opioid use may lead to an increased
8 mortality, and we need to keep in mind the risk of
9 underdosing as well as overdosing.

10 DR. BROWN: Dr. Shoben?

11 DR. SHO BEN: Abby Shoben. I am also a
12 biostatistician, not a clinician. But I wanted to
13 echo some of Dr. Bateman's comments about the risk
14 for adolescents in particular. And that the
15 presentation from Dr. Levy talking about how they
16 may be at sort of greater risk of drug abuse and
17 drug misuse and whatnot suggests that perhaps
18 overtreating in that patient population is a
19 primary concern.

20 This idea of giving them prophylactic type
21 prescriptions that we heard about with the
22 orthopedists might be particularly dangerous in the

1 adolescent population. But with the younger group
2 where you're worried about long-term, making them
3 more sensitized to pain and things, you might
4 actually be more worried about undertreating.

5 So I think this general, all pediatric
6 patients, the risk may be different for different
7 ages as we've heard, but just in particular the
8 adolescent group is at most risk for this
9 overtreating problem.

10 DR. BROWN: Dr. Czaja?

11 DR. CZAJA: Angela Czaja. This is building
12 off a little bit of Dr. Kibbe's statement. It's
13 interesting that the second half of our first
14 question is about the safety of the study of
15 opioids, because the reality is they're all being
16 used right now, and we're just not actually
17 studying it in individual patients.

18 So I think later down our discussion line is
19 creative ways of leveraging how we can study this
20 as we are already using it now. To me it seems a
21 bit artificial to say should we study it because
22 we're already using it, and we just need to

1 understand better from how we're using it, the
2 safety and effectiveness of things.

3 DR. BROWN: Dr. Neville?

4 DR. NEVILLE: And just to build on that, and
5 echo, and reiterate what we heard yesterday, I
6 think we do need to be very careful about adverse
7 events and the increased risk of addiction in
8 adolescents. But the data show that misuse and
9 abuse is coming from the medicine cabinet largely,
10 not from opioids that are being prescribed to the
11 actual pediatric patient.

12 So I think we need to keep that in mind as
13 we're talking about patient selection and
14 management because it's not the patients who are
15 being selected and managed largely who are the ones
16 who are currently overdosing and misusing drug,
17 it's from the adult population and what's in the
18 medicine cabinet or coming from the school locker.

19 DR. BROWN: Dr. Hertz?

20 DR. HERTZ: Yes, thank you. It's always
21 hard to figure out how to word questions to try and
22 get the information that we're seeking. And I'd

1 like to just maybe reconfigure perhaps even
2 questions 1 and 2 together in a slightly different
3 way.

4 In the context of studying opioids in
5 children with pain, perhaps breaking it down by
6 adolescents, middle-aged children, and then the
7 most young, and then also thinking about the
8 context of using it in the acute perioperative or
9 acute period versus in somewhat longer periods,
10 which from the data we have seems to be more in the
11 order of weeks than months for most kids, although
12 clearly there's some chronically active pain
13 conditions.

14 As I think you may be aware from some
15 comments or from some press coverage, there's a lot
16 of fear about opioid use. And there's a lot of
17 statements that are reflective of that fear, like
18 we don't have information about efficacy.

19 We have information about efficacy. Our
20 clinical trials may only be 12 weeks in duration,
21 but many of these patients have been on opioids for
22 months or years prior. They get randomized into a

1 trial, and it shows in fact that the opioids
2 continue to work.

3 The fact that we get small treatment effects
4 is not evidence that opioids don't work. I think
5 anyone here who has ever had pain and has taken an
6 analgesic knows that there's an effect. But in the
7 context of a clinical trial, trying to understand
8 that effect across a population with many
9 variables -- not the least of which is individual
10 variability to the effects of different opioids
11 based on our own individual mu opioid receptor
12 subtypes and other factors -- will influence an
13 understanding of efficacy in a population.

14 If we understand that there's a lack of
15 understanding of the available data on efficacy,
16 that there is clearly a problem in terms of how
17 opioids are used in a very broad sense in
18 adults -- and in a bigger issue, we heard that pain
19 management in general in adults is not well done in
20 this country for a variety of reasons, being
21 predominately prescription based and not looking at
22 a multimodal/multi interdisciplinary approach, is

1 the environment in which we're having this meeting.

2 What I would like to know is, what we would
3 like to know, we recognize the need to have data
4 for clinicians. Congress recognized it when they
5 gave us regulation and legislation.

6 So in the context of studying these
7 different age groups and the settings in which
8 their management is relevant -- so a lot more
9 emphasis on acute in the youngest with a little bit
10 more longer term, although not a lot for the older
11 groups -- are there particular safety
12 considerations based on age or circumstance that
13 you've either encountered in your clinical practice
14 or are aware of from presentations, or other
15 general experiences that you've had, that we should
16 be thinking about as we plan these studies?

17 For instance, one thing I'm hearing very
18 clearly is longer term follow-up. And when we're
19 talking about that, it sounds like so far what I'm
20 hearing is an interest in longer term follow-up,
21 both on neuro developmental effects when the
22 exposures occur in the most young, as well as

1 effects on future development of both responses to
2 pain and risk for addiction.

3 So are there other things? I'm also hearing
4 about the importance of acute safety, understanding
5 that initial PK/PD in the acute setting for these
6 different opioid substances.

7 So these are the sorts of things that I've
8 heard so far. Are there other areas in this, very
9 specific safety related issues in these
10 populations -- which I will now say, rather than
11 calling the pediatric population, but in these
12 pediatric populations -- that should be taken into
13 consideration as we plan these clinical studies?

14 You can even go so far, if you think it's
15 appropriate, to talk about drug substance versus
16 formulation, IR versus ER, parenterals, anything
17 that you think might be an important factor to take
18 into consideration from the safety side. And we'll
19 talk a little bit more about efficacy as well, but
20 for now anything else that we can glean about what
21 we should be doing better to study the safety.

22 DR. BROWN: Dr. Hertz, let me ask a question

1 by way of clarifying what you're saying. There was
2 substantial discussion yesterday and today, and
3 every day for the last little bit, about the impact
4 of the adolescent central nervous system and the
5 development of the nervous system from age 11 up to
6 some people would say age 25. And Dr. Levy very
7 elegantly gave us information about that, some of
8 which was new to many people.

9 So that would be an area of focus where
10 there would be an individual, an identified
11 individual safety concern that I would see. Do you
12 see that as one of the things that you were looking
13 for, or has that already been incorporated? Do we
14 need to talk about that anymore?

15 DR. HERTZ: I think that right now I
16 wouldn't say anything's been covered adequately.
17 I'd like to hear as many comments, because it gives
18 me a sense of the things that are on the minds of
19 these committee members, of all of you, and the
20 relative importance of different aspects of safety
21 data that need to be collected.

22 I mean, let's face it. We're here because

1 we know that there's just a real paucity of data.
2 And not that we ever thought it would be simple,
3 but I think we didn't adequately provide space for
4 the complexities and the questions.

5 So, given that, yes, but that's the kind of
6 thing. So what do you think we need to do?

7 Dr. Levy provided background for why adolescents
8 may be at greater risk, and she mentioned one
9 study, that she had some others that she could send
10 us.

11 Do you want more data on that? Is there
12 some aspect of the risk in adolescents prescribed
13 opioids that you want us to consider further? If
14 you have a sense of how long we should be following
15 these children.

16 We don't have the power to construct the
17 type of consortia that you're discussing, but what
18 we can do is require these data be collected, which
19 could then stimulate the interest among companies
20 who have to fulfill these requirements to look for
21 ways to do it. And they may come to experts in the
22 field to try and get the resources in place.

1 Right now, it doesn't have to be something
2 that's inherently doable; it has to be something
3 that's inherently necessary to get. And then once
4 we have the requirement, we can try and stimulate,
5 through our authority over industry, for them to
6 get that work done.

7 DR. BROWN: I'm going to make one more
8 comment about what you were talking about, and then
9 I'll shut up and let everybody else talk. But this
10 past week, there was a discussion in Bethesda about
11 research in pediatrics. And one of the interesting
12 topics was on formulation of drugs, and it's
13 something that we haven't really considered very
14 well here.

15 As I think about safety concerns and
16 pediatric patients, and small volumes given to
17 ambulatory patients, one of the real issues that I
18 can see is some determination about do certain
19 drugs need to be reformulated in a way that makes
20 them safer and studied in that regard or not?

21 DR. HERTZ: So part of the requirements that
22 we place on companies in conjunction with the

1 requirement to do pediatric studies is for the
2 development of age appropriate formulations. And
3 that goes so far as to require a demonstration of
4 why they are unable to develop appropriate
5 formulations if that's what they're going to
6 respond back to us.

7 For instance, can the dosage form be made
8 appropriate for a particular age range? Obviously,
9 we're not going to give an infant a large capsule.
10 Or what are the limitations on something that's
11 either extended release or a transdermal? What are
12 the limitations there with regard to different age
13 groups? We will work with companies to ensure that
14 due diligence is given to creating a
15 pediatric-specific formulation.

16 If there's other aspects of that, from a
17 safety perspective, that you want to comment on,
18 you can as well. But we already are trying to do
19 things like require for liquid formulations, that
20 they be configured with a syringe, so that the
21 teaspoon thing is minimized, meaning that someone
22 taking a teaspoon out of drawer from their set of

1 silverware is not the measuring tool -- we all know
2 that's a challenge -- and that the ability to
3 deliver the intended dose is feasible, for instance
4 in the setting of an oral solution.

5 Some of that we have separate ability to
6 require. So really, in terms of formulation, it's
7 about creating something that's suitable for study
8 in the population that we think may benefit from
9 using it.

10 DR. BROWN: The only other comment I would
11 make was that there was some discussion about the
12 distribution of active drug in individual
13 formulations. For children, this is
14 mostly -- we're usually talking about a liquid
15 form, but not routinely. So just a shout out to
16 that. The expectation that the distribution of
17 drug within a tablet or pill is not uniform unless
18 it's scored. I know I'm preaching to the choir
19 here.

20 DR. HERTZ: Yes, we would cover that. If a
21 lower dose, lower strength was to be developed,
22 such that there's a small amount of active opioid

1 within a larger matrix of excipients making it into
2 a pill, we have different chemistry manufacturing
3 and control requirements for content uniformity,
4 testing.

5 We will cover that piece of it. We'll make
6 sure that if a pediatric-specific formulation is
7 developed, that it meets the standards for
8 delivering a quality product. That part we're good
9 on. We have that expertise.

10 What we would really like to hear, what I'd
11 like to hear perhaps a little bit more, is if
12 there's other areas of the safety aspects in these
13 different populations of interest to you that we
14 should be incorporating into our studies based on
15 clinical experience, things you've heard, concerns
16 that have been raised.

17 DR. BROWN: And pursuant to Dr. Hertz's
18 request going forward, are there any specific
19 comments that relate pretty specifically to what
20 she has just asked for? Dr. Crawford?

21 DR. CRAWFORD: Thank you.
22 Stephanie Crawford. I'm going to change something

1 I would have stated earlier before you so kindly
2 specified more of what you were asking about. I do
3 want to make one statement, though, in the record
4 in respect to something we heard in the open public
5 hearing about essentially how can you think about
6 studies for this pediatric population, just to
7 state for the record, because these studies,
8 vulnerable children any time are going to be
9 extraordinary safeguards. Any studies undertaken
10 will be under an institutional review board, and
11 usually a data safety monitoring board in addition.

12 In terms of safety, in addition to what
13 we've heard about the importance of the safety
14 profile, be it blood or urine, for this population,
15 one of the things -- the medical histories are
16 taken with all the patients that are in studies.
17 In addition, the social history, one of the things
18 I wonder is, if pain is not controlled for the
19 associated conditions, will there be more
20 depression, then is that also treated; anxiety or
21 other issues.

22 So it might be safety profiles even beyond

1 the drug under testing, for adolescent populations
2 in particular, if they don't feel they could get
3 these opioids through the established channels, be
4 it in a study -- well, they would in a study, but
5 otherwise where are they getting it? Are they
6 getting it more? To really be asking that
7 qualitative data, part of the history with that.

8 Are you going to the internet? It's far
9 better if we can get something that's controlled
10 through the U.S. medication system, family,
11 friends, others. In terms of trials, we know the
12 limitations, so I think we should also be
13 considering pragmatic trials for effectiveness in
14 the real world.

15 The point you were making, Dr. Hertz, about
16 the formulations is very interesting. I do not
17 know if it's something FDA does, but there would be
18 compounded preparations. So if the regulated
19 industry states it's not possible to give specific
20 pediatric formulations, perhaps there should be
21 some kind of stakeholder group between the
22 pharmaceutical industry outsourcing facilities, and

1 perhaps voice of pharmacies, representatives who
2 would do compounded preparations just to make sure
3 it's a very good product that's dispensed to the
4 patients.

5 DR. BROWN: Dr. Ruha?

6 DR. RUHA: Is this from when this was up
7 before?

8 (Laughter.)

9 DR. RUHA: I'm not sure that it's even
10 stating the obvious, but this goes back earlier
11 when we were just discussing like safety concerns.
12 I was just trying to broaden my interpretation of
13 the question, but safety concerns around the study
14 of opioids.

15 We've been talking about studying opioids
16 that we're already using in children, getting more
17 safety data on them, which makes a lot of sense.
18 But I don't know if there's any consideration of
19 going forward if new opioids were to be developed.
20 And I'm assuming that we would still study those
21 first in adults and get the safety data in adults,
22 and not ask for simultaneous study in children.

1 DR. BROWN: Dr. Hertz, go.

2 DR. HERTZ: Yes.

3 (Laughter.)

4 DR. BROWN: Dr. Patrick?

5 DR. PATRICK: I wanted to specifically
6 address some of the questions that Dr. Hertz
7 mentioned before. So as an example, methadone is a
8 common drug that we use for neonatal abstinence
9 syndrome. About 20 percent of infants with NAS
10 nationwide are treated with it.

11 There are significant concerns about alcohol
12 in that preparation. There are still questions
13 about QT prolongation. I'm not saying I have an
14 answer. There are some studies that suggest that
15 it actually may decrease length of stay. There's
16 just a lot of unanswered questions.

17 Along those lines, I think some of the
18 questions -- even had a discussion with a colleague
19 this week about prolonged opioid weans
20 inpatient/outpatient. What does that mean for
21 long-term development? In some of our work and in
22 some of the literature, we see that when infants

1 are discharged home on opioid weans, sometimes it
2 can go on for months. And what does that mean for
3 development versus the undertreatment of withdrawal
4 signs? So I think that there's a lot that we don't
5 know there still.

6 Then just back to the pre-term issue, I
7 think one of the issues that we have -- and it goes
8 back to some of the points that were made before,
9 which is what does pain look like in a 25-weeker?
10 It's pretty common for me to show up in the morning
11 or whatever and see a very small infant on a
12 fentanyl drip. And I am just not sure what that
13 means long term. It's good intentions, right,
14 you're trying to treat pain, but what does that
15 mean?

16 There's so much that needs to be understood
17 and developed about the trade-offs of untreated
18 pain in pre-term infants, particularly extremely
19 low pre-term infants, and how do we sort of weigh
20 those safety concerns and what those mean for both
21 pre-term infants and just infants in pain, as well
22 as those that are having withdrawal? It's an

1 amazing amount of data gap that are there, and I
2 think it's a part of what we need to strive for
3 moving forward.

4 DR. BROWN: Dr. Turer?

5 DR. TURER: One thing that struck me is part
6 of the conversation is should these be studied in
7 children? Can data be extrapolated from adults?
8 And I think it's striking how much the conditions
9 in children differ from those in adults for which
10 we use pain medications.

11 So I do think that it bears studying these
12 in kids. But in order to do that, I think we need
13 a taxonomy of what are the specific pediatric
14 conditions, which you were getting at. What are
15 the specific populations that are at unique risk?
16 So you define the premature, the low birth weight.
17 You define those who are undergoing tonsillectomy
18 and adenoidectomy. And kids with obesity I think
19 are a specific population that are at risk, or more
20 likely to fracture.

21 So conditions of pain, but then also
22 settings that incur pain. And then for each of

1 those, define what are the short-term benefits, the
2 short-term risks, the long-term benefits, the long-
3 term risks? How do we measure each of those?

4 We need specific methodologies. It's very
5 challenging to sort out children who are
6 25-weekers, when are they in pain. How do we
7 define pain in those kids? And it's going to be
8 very, very different from the adolescents.

9 So we need the methodologies. We need the
10 populations. And then the data avenues, you know
11 how do we get at that information comes from that.
12 And then the consideration of the range of
13 modalities to treat each. So that includes the
14 formulations, the preparations that would be
15 applicable to each and wouldn't be limited to
16 opioids.

17 I know that some of these algorithms exist
18 in pediatrics. They certainly do in adults, with
19 like low back pain. But I think that may allow a
20 roadmap to be formed, and then for the evidence for
21 each of those components to be filled in and help
22 us better determine safety based on risk/benefit

1 ratios.

2 DR. BROWN: Dr. Kaye?

3 DR. KAYE: Alan Kaye from LSU. I have three
4 suggestions for the FDA. So yesterday, number one,
5 we were told 84.2 percent of opioids were obtained
6 by adolescents. They were given by or taken from a
7 family member or peer. Everyone who is given an
8 opiate signs an opiate agreement.

9 The FDA can advocate for a secure place, a
10 box, something, and ask providers to document with
11 a picture or something, have them sign in the
12 agreement, so that the access for adolescents would
13 be greatly diminished. I think that's easy. We
14 already have an opiate agreement. We just have to
15 firm it up and document that the opiates are not
16 accessible to adolescents.

17 Number two. We're talking about getting
18 some data, and I think that we can use pharmacy
19 data and develop a simple protocol or protocols,
20 and basically reach out to those pediatricians that
21 are prescribing these opiates, and provide perhaps
22 a little grant or incentive for them so that we can

1 get some good pharmacologic data that would be
2 helpful for everyone in the country and worldwide.
3 I think that's at least a step forward to the
4 question of getting some data.

5 And the third to Dr. White's point, I think
6 it's a great idea to embed and get other opiate
7 data through existing studies, and we can do that
8 through communication. The FDA can communicate
9 with IRB heads who can scan existing protocols and
10 see what would be reasonable to embed within these
11 existing studies that are already IRB approved, so
12 that we can get further information where we're so
13 lacking in it at the present time.

14 My last comment is just from a pharmacology
15 point of view. For oral medications, when we're
16 looking at steady states, we need to have 5 doses.
17 So that may be a little different than some of the
18 acute situations where opiates are prescribed.

19 Thanks.

20 DR. BROWN: Dr. Bateman?

21 DR. BATEMAN: Yesterday in Dr. Berde's
22 presentation, he talked about a downside of the

1 neuroplasticity that is inherent in this group.
2 And that is something that, at least in animal
3 models, the neuroplasticity leads to more rapid
4 tolerance and more rapid development of
5 opioid-induced hyper analgesia. So I think when
6 we're looking at longer term studies of these
7 opioids in the pediatric population, being really
8 attentive to those two endpoints will be quite
9 important to safety considerations.

10 DR. BROWN: Dr. Walco?

11 DR. WALCO: In response to the issues that
12 you were raising, Dr. Hertz, I think what's going
13 through my mind is separating the issues of
14 internal validity and external validity in study
15 design. And most clinical trials are designed to
16 maximize on internal validity, that is specifically
17 looking at the effect of a drug versus some
18 comparison, and looking at related side effects,
19 et cetera. But you then limit the ability to
20 generalize to how that drug will be used in the
21 real world.

22 It sounds to me from the discussions we've

1 had that a huge part of the problem here is
2 prescribing, and not necessarily how the drug
3 behaves. So I think there's a compelling reason,
4 for example, to study how opioids may be used in
5 young children, 6 to 24 months, data that we don't
6 currently have. And that would be very worthwhile
7 to understand the safety and the efficacy of
8 various drugs.

9 The relationship between doing that study
10 and preventing accidental deaths from overdose in
11 adolescents and young adults, in my mind is a very
12 large disconnect. So I think that it really would
13 be important to keep the issues separate.

14 To say that we want to maximize internal
15 validity and understand how these drugs behave in
16 different formulations, et cetera, is important
17 work to be done, and it's important to understand
18 how to curb what's going on with the accidental
19 deaths, but I really don't see how those can be so
20 connected the way it's being asked in questions 1
21 and 2. I think they're both great questions, but
22 it's not the same question.

1 DR. BROWN: Dr. Lasky?

2 DR. LASKY: Thank you. So I'm also trying
3 to address Dr. Hertz's point about endpoints. And
4 I'm thinking that you're looking for ideas of
5 safety endpoints in designing clinical trials. And
6 some of the more obvious ones are the ones that
7 more readily come to mind have been mentioned. And
8 there's a kind of circular issue. When an area
9 hasn't been studied well, we really don't know what
10 the safety endpoints are, and at the same time we
11 have to specify them when we're designing the
12 clinical trials.

13 I don't know if this is the kind of
14 suggestion you would be looking for, but one is
15 obviously, or maybe not so obviously, a systematic
16 literature review to identify endpoints that
17 haven't come up in the conversation because we're
18 probably focusing on the ones that are foremost in
19 our minds.

20 But also something, which I don't think I've
21 ever recommended, which is to look at case reports.
22 Because in this kind of body of literature, case

1 reports may turn up endpoints that are rarer, but
2 at least worth reading the case reports. Because
3 people know about the well-known safety endpoints,
4 and we don't know about the lesser known safety
5 endpoints, potential endpoints.

6 DR. BROWN: Dr. Hoehn?

7 DR. HOEHN: I have three comments in
8 reference to what Dr. Hertz was saying. So one is
9 in terms of specific information I think we need
10 more of from a clinical perspective. I certainly
11 feel like we need more in terms of pharmacokinetic
12 data and how toddlers metabolize things. We've
13 talked a lot about the micro preemie, the extremely
14 low birth weight and adolescents. But clinically,
15 it seems like the toddlers are the ones that have
16 the tachyphylaxis and end up on the highest doses
17 of narcotics in the shortest period of time. And
18 they're the same ones that also seem to have
19 delirium after they get off of the high doses and
20 things like that.

21 So I think a specific question, or a
22 specific answer to the question about what are some

1 safety concerns, I think why toddlers have such a
2 faster metabolism than everybody else, would be one
3 safety question.

4 Then a second one, as Dr. Hertz, when you
5 were talking about what you can regulate and what
6 you can't, I didn't know if the industry -- not for
7 new drugs but for old drugs, if industry could be
8 forced to put together some sort of a database,
9 similar to the ELSO database for people who go on
10 ECMO, where people are just required to. If you're
11 going to do a narcotic, you have to say what was
12 the diagnosis, what was the date, what was the
13 duration?

14 I mean, it certainly seems as though similar
15 databases exist. If you look at Accutane, I'm sure
16 the government could pull the data tomorrow on who
17 got what dose of Accutane for how long. So it
18 seems like there's ways that either the FDA or
19 industry could be forced to put together some
20 database, even just with diagnosis, weight, and
21 duration of dosage, and looking at some of the side
22 effects there; not some huge elaborate multi-center

1 study, but just sort of collecting data that then
2 people could look at.

3 Like I said, similar to Accutane, there's
4 ways that those things could be regulated more
5 closely. That was my third comment. That was the
6 same thing. Sorry, two and three are the same.

7 I was thinking about what Dr. Kaye said
8 about regulating opioids a little bit more closely
9 in terms of the pain contract. And just going
10 through what we just went through to get my
11 13-year-old on Accutane, clearly there are
12 mechanisms that exist to have people sign their
13 life away before they get a medication.

14 Then following up on what Dr. Levy was
15 saying from yesterday, that all the adolescents are
16 getting from someone else's meds. It's just a way
17 to sort of tie it together. And that was my only
18 thinking, is that there's clearly precedence for
19 higher levels of regulation for other types of
20 medications.

21 DR. BROWN: Dr. Neville?

22 DR. NEVILLE: And I'm not sure if I'm going

1 to answer your question, Dr. Hertz, but I'm going
2 to try, at least from my perspective. But to echo
3 what Dr. Hoehn said, as you all know, we use
4 Accutane for neuroblastoma. So there's also quite
5 rigid requirements on a prescriber, and I myself
6 have thought the same thing, that why couldn't that
7 be applied to opiates.

8 I know there is a lot of politics because
9 it's state by state, but some sort of federally
10 mandated way to keep of track would be very
11 helpful. And you could require education much the
12 way that it's required in a registration system,
13 much the way it's required for prescribers of
14 Accutane.

15 But to answer the question, one, if we want
16 to talk about specific patient populations, and
17 obviously I'm biased because I'm a
18 hematologist/oncologist, but one of the patient
19 populations I worry a lot about is the sickle cell
20 patient population. Because even though, with the
21 advent of hydroxyurea, pain crises have diminished,
22 we still use a fair bit of opiates. And there is

1 some evidence that during puberty, especially for
2 girls, pain crises increase. So we don't know what
3 happens to those patients when they go in the adult
4 world.

5 To Dr. Hudak's point yesterday, I would
6 advocate for increasing the age of what we consider
7 pediatrics, because we don't know -- you know, you
8 hear a lot in the field about pseudo addiction, but
9 I don't know the data on how many patients with
10 sickle cell disease who we treated as adolescents
11 become addicted as adults.

12 Also, we're curing more cancer, so patients,
13 adolescent cancer patients who are getting
14 narcotics along with their chemotherapy what
15 happens, we have long-term survivor programs, so do
16 they have increased sensitivity to pain? Do they
17 have misuse, addiction problems? I think those are
18 two patient populations that could be fairly easily
19 studied, and that we currently, that I know of,
20 don't have data on.

21 I would also echo what Dr. Kaye said about
22 the return of the drugs. Because I do early phase,

1 I do a lot of end-of-life care, and I prescribe a
2 fair bit of narcotics. And I had trouble finding a
3 place where the family could get rid of them, and I
4 was told I was not allowed to take them back.

5 Again, it's state regulated, but there's no
6 good, easy mechanism to take back drugs, or to even
7 keep track of what a family has in the house, even
8 at the end of life. So I ended up sitting there
9 saying, holy cow, am I contributing to the problem
10 because my patient died sooner than I expected, so
11 there are narcotics in that house that someone else
12 is going to misuse.

13 I think that agency could advocate and work
14 with DEA to help us, who are prescribers, better
15 keep track in more of an educational than punitive
16 way, and to facilitate the return of drugs, even if
17 it's back to the provider, to decrease that pool.
18 And I know that's a little off your question, but I
19 think it does go to the safety and misuse.

20 DR. BROWN: Dr. Harralson?

21 DR. HARRALSON: We talked a little bit about
22 how in the neonate you have developing enzymatic

1 systems, and that can present some real problems.
2 We didn't mention, though, that they also have
3 impaired renal function, and a lot of the
4 metabolites of the opiates are renally excreted,
5 and so you have sort of a double issue there.

6 If you're going to study the kinetics in the
7 neonate, you have to consider the full range of the
8 parent drug and the metabolites to understand how
9 that may be impacting respiratory depression,
10 because we know some of the glucuronide
11 metabolites, for example with morphine, are active.
12 And so that would have to be included, whereas in
13 older children and adults, it's only an issue if
14 they have renal impairment.

15 DR. BROWN: Dr. Tyler is on the phone.
16 Dr. Tyler, do you have a question?

17 DR. TYLER: I had a comment. This is a blue
18 sky type of comment. Is there a way to standardize
19 how we monitor patients for efficacy and safety?
20 It would have to be an opportunistic, pragmatic
21 outcomes type study. We're using the drugs; we
22 have to figure out how to snag the information, not

1 in the detailed way we would for an RCT, but in a
2 way that we would monitor in clinical practice.

3 We could have age appropriate monitoring to
4 snag what we're worried about for each age group.
5 We would also need differences between acute and
6 chronic use. If we were able to standardize it,
7 then we can leverage our EMRs and work with our EMR
8 vendors. But the bottom line is, we have to figure
9 out a way to snag the data from our daily clinical
10 practice.

11 DR. BROWN: Thank you, Dr. Tyler.

12 Dr. McCann?

13 DR. MCCANN: Dr. McCann from Boston
14 Children's. To get to your safety question, I was
15 thinking about how we handle narcotics in
16 ambulatory surgery in babies again. So at Boston
17 Children's Hospital, if you require additional
18 narcotics in the recovery room, and you're under
19 3 months of age, you automatically get admitted.
20 If you're under 6 months of age, you're strongly
21 encourage the surgeons to admit them. We don't
22 like to send these patients home with narcotics.

1 It struck me that you might get some
2 information if you queried program directors of
3 children's hospitals as to what their policies are,
4 and the reasons behind their policies. And that
5 might be able to -- that would help you, I would
6 think, to design studies to further answer the
7 question.

8 DR. BROWN: Dr. Maxwell?

9 DR. MAXWELL: I think that we're all aware
10 that there are vulnerable populations in terms of
11 acute opioid administration in the post-operative
12 period, and when clinical trials are designed,
13 frequently those vulnerable populations are
14 excluded. I'm talking about children with
15 congenital abnormalities, neuromuscular disease,
16 airway abnormalities, and other conditions, which
17 may increase the risk of respiratory depression
18 with the use of opioids.

19 But these are the populations we need to
20 know more about, and who frequently get under dosed
21 for pain. They don't have an absence of pain, they
22 have an elevated concern, which is not based on

1 data, that they're more at risk for adverse events.
2 And I think that we need to find a way to study
3 these populations.

4 There are data that exist that are based on
5 surveillance systems in hospitals, either based on
6 surveillance of monitoring data, looking for acute
7 events, or rapid response team calls, or code team
8 calls that have been published that tie critical
9 events, either airway events or cardiac arrest, to
10 opioid administration. Some hospitals also monitor
11 naloxone administration.

12 These data are available, but with a very
13 low denominator and a small number of events. But
14 it is a way that we could use our electronic
15 medical record and our monitoring systems -- I know
16 Mayo has an event monitoring system -- in order to
17 detect signals in either at-risk populations or to
18 know what the incidence of actual events are with
19 opioid administration in our institutions.

20 DR. BROWN: Dr. White?

21 DR. WHITE: Thank you. Michael White,
22 New Orleans. I'm going to ask you to bear with me

1 for a few minutes. My mind gets a little bit
2 scattered when we're dealing with so many different
3 subjects. With respect to the neonatal follow-up
4 for children that are using methadone for weaning,
5 it strikes me there are two separate populations
6 that one worries about there.

7 One would be the iatrogenic addiction that
8 may occur when you have children on ventilators for
9 long periods of time, or in discomfort for whatever
10 reasons. Those children are intrinsically
11 different from children that are on methadone
12 because the mother was taking some narcotic. I
13 mean, the children that come in where the mother is
14 taking narcotics, there are frequently other drugs
15 that are involved in that circumstance, and they
16 may not be the same neurologically stable. That's
17 not the right word. The substrate, the
18 neurological substrate is probably different in
19 those two groups.

20 The other problem that one's going to need
21 to sort out is the problem that we have babies in
22 neonatal intensive care units, and we know the

1 development of children in neonatal intensive care
2 units and the way they interact with their parents
3 after discharge, or even while they're in the
4 units, are very different from children that are
5 exposed to their parents from the get-go, from the
6 start.

7 Also, in these two disparate groups, we have
8 the neonatal intensive care unit, and the one whose
9 parents, where the mother might have been an abuser
10 of drugs, quite frequently those fall into child
11 protective cases. Those children frequently will
12 wind up in foster care for some period of time, and
13 the interaction between mothers who are using drugs
14 and mothers who are not. They're going to be so
15 many confounding factors, I'm just really not sure
16 how one's going to be able to tease out the effect
17 of the narcotics in that group.

18 Then if we move to the adolescents, there
19 was some nice materials -- the briefing materials
20 included several studies looking at non-medical use
21 of narcotics, prescription narcotics. And if you
22 look at that, the numbers have gone down

1 significantly. There's about a 30 percent decrease
2 in non-medical use of prescription narcotics in
3 adolescents and young adults since 2002. The
4 trends are down in both the major studies they
5 presented to us.

6 The problem we have in doing long-term
7 follow-up in that group of patients is that the
8 patients that are most likely to be using medical
9 narcotics outside of prescription, the way they
10 should be, are those that are also participating in
11 other high-risk behaviors.

12 We can look at it, and they're the same
13 children that was pointed out yesterday: smoking,
14 using alcohol, et cetera, et cetera. They're
15 usually from single-parent households. They're
16 usually performing poorly in school. It's a high
17 incidence of use in young female subjects, not
18 subjects but children, adolescents, that have major
19 depressive disorders.

20 Again, long-term follow-up for what is the
21 effect of narcotic above the underlying substrate
22 of disability, alternative behavior, and such, is

1 going to be very difficult to tease out,
2 particularly since we don't have large population
3 databases to compare, and we have no controls for
4 these sorts of behaviors.

5 So as much as I would like to see some
6 long-term follow-up and see if we could figure it
7 out, I think that statistical evaluation is going
8 to be quite difficult to get around these
9 confounding factors, but look forward to seeing how
10 we manage to do that.

11 DR. BROWN: Dr. Havens?

12 DR. HAVENS: Thank you. Peter Havens. I
13 greatly appreciate Dr. Hertz's statement that we
14 need more data and asking specific questions about
15 age groups and outcomes. It strikes me during the
16 conversation, that the age groups of interest are
17 premature infants separate from term to age
18 3 months; that the 3 month to 2 year age group is
19 perhaps special; that 2 to 12 years, again,
20 likewise is special; and over age 12, the risks and
21 potential benefits are different.

22 The premature infants have a different

1 reason for use than many of the other groups. It's
2 more difficult to establish short-term benefit
3 potentially in the ICU type setting. But the
4 outcome of interest in that context may be
5 long-term neuro development and neurotoxicity
6 concerning issues relating to apoptosis and overall
7 brain development.

8 In the term to 3 month newborn, issues
9 related to acute surgical care and the safety in a
10 post-operative period, as we just heard from the
11 Children's in Boston perspective, if you get an
12 extra dose, you stay in the hospital, it brings up
13 this issue of the duration of pain, and its
14 potentially changing aspects over the age range.

15 Partly, however, this may just be related to
16 our inability to truly measure the physiologic
17 impact of pain and its outer manifestations, so we
18 need to be careful about that. But in the term to
19 3-month group, there's both acute issues as well,
20 potentially, as long-term issues, not just with
21 neuro development, perhaps less so than in the
22 preemie, but in terms of later pain

1 hypersensitivity, as we heard from before.

2 In the 3-month to 2-year age group, I think,
3 again, dosing and actual need, again, now we look
4 at -- in the matrix that you might develop, a lot
5 of this might be in acute post-op or outpatient
6 surgery, or fractures for example, and whether or
7 not narcotics are even needed, or again the
8 duration of an ability to show a benefit of
9 narcotics compared to other analgesics.

10 Likewise in the 2 to 12-year-old age group,
11 the dosing becomes an important issue, and whether
12 or not you really need them at all, or how long,
13 that you see a benefit from narcotics becomes an
14 acute issue.

15 Then finally in the adolescent, again the
16 orthopedic discussion yesterday was excellent in
17 terms of the sort of randomness of how long they
18 would be prescribed, so what is the duration of
19 benefit that you might see. And then this leads
20 more into that adolescent age group discussion of
21 the potential for later abuse.

22 So I appreciate the specificity of your

1 questions. I hope the specificity of my answers
2 was not irritating.

3 DR. BROWN: Dr. Hudak?

4 DR. HUDAK: Yes. I would like to return to
5 neonates a bit and echo sentiment of others that
6 this is a whole separate area. And even Dr. Havens
7 just said, 25-weekers are very different than term
8 babies. I do think that this is a field that many
9 of us have struggled in for a long time. I think
10 we're caught between things we have to do and
11 things that are possibly unknowable.

12 I'd like to make a couple comments. One is,
13 perhaps safety needs to be looked at not in an
14 absolute fashion, but comparatively. So for
15 instance, you know we deal with the problem of
16 neonatal abstinence where a fetus is basically
17 bathed in an environment rich with opioids and
18 other substances. So that's one of the reasons why
19 it's very difficult to determine a specific effect
20 of opioids on infant and child development.

21 But perhaps, I mean one thing to look at
22 would be, since we do have these mothers in opioid

1 maintenance programs, whether or not there is a
2 difference in long-term outcomes in these children
3 if the mother is on buprenorphine versus methadone,
4 for instance, which has not really been
5 established, and which is I think a critical public
6 health issue. So that would be a comparative
7 safety analysis that could be done.

8 The other issue in term babies, we use
9 opioids very differently from nursery to nursery
10 across the range of gestational ages, prompted by
11 different concerns, prompted by different
12 interactions with our staff, prompted by different
13 interactions with our parents. So there's
14 tremendous variability.

15 I certainly cannot tell whether a child who
16 is 45 weeks is in pain or not. I can try to assess
17 that. If the child is tachycardic, I try to make
18 sure that the child's not hypovolemic. If the
19 child is not hypovolemic, I might try a dose in an
20 at-risk child to see if there's a decrease in heart
21 rate. But we really don't have a good assessment
22 of pain, so I think it would be very difficult to

1 study.

2 On the other hand, we have the phenomenon of
3 term babies who are on therapies like ECMO, or
4 post-operative pain relief, where we know there are
5 issues. These children are treated with opioid
6 infusions. Comparatively, we don't know whether
7 fentanyl, for instance, or morphine is a more
8 effective treatment. My observation, which may be
9 flawed, is that we tend to escalate fentanyl much
10 more quickly than we do morphine infusions.

11 I'm managing long distance a child now who
12 is on day 14 of ECMO. We are up to 5 micrograms
13 per kilogram per hour of fentanyl. We started at
14 1. We are on intermittent Denzo boluses. We are
15 on 1 microgram per kilogram per hour of Precedex.
16 We are on phenobarbital. And all of these things
17 are necessary to make sure that this child doesn't
18 sort of bounce off the bed and decannulate himself,
19 which would be a fatal event. We don't want to use
20 paralytics in these kids because that compromises
21 pulmonary toilet.

22 So we're in a rock and a hard place in a lot

1 of these babies, and I think perhaps the things we
2 need to study in these babies are things to do with
3 the pharmacokinetics of these medications, why is
4 it for instance that these babies have different
5 rates of becoming tolerant, and look at comparative
6 short and longer term safety and development issues
7 of, for instance, morphine versus fentanyl.

8 So I think with particular respect to any
9 particular agent, we may find a very limited amount
10 of information we can get. Certainly PK
11 information would be helpful. The variability by
12 genotype would be helpful. But at the end of the
13 day, maybe the best we can do, since these are
14 drugs we have to use, there being no other
15 alternatives, are maybe comparative safety
16 analyses, and I think that needs to be factored
17 into the thinking.

18 DR. BROWN: We're going to take a break now,
19 but before we do, I'm going to try my best to
20 summarize at least some of what I've heard from the
21 experts around the table this morning. I hope that
22 if I miss a specific overriding issue, that you

1 will let me know about it, and quite honestly, I'm
2 sure you will.

3 This is a special time in history where we
4 have a public health issue, which both produces
5 dangerous overtreatment of some patients with
6 consequences, and it also has the possibility of
7 producing profound undertreatment. Undertreatment
8 in and of itself has profound effects that are not
9 advertised to the extent that opioid deaths are.

10 We will be using opioids in children for the
11 foreseeable future. We need to understand the key
12 issues around these drugs, both in the acute realm
13 and in patients with more chronic disease
14 processes.

15 There is some concern, and it's largely why
16 we're here, that the current fear relating to abuse
17 and addiction in adults, and in children to some
18 extent, will affect the agency's ability to make a
19 rational judgment about the balance of providing
20 pain control for children and making children safe
21 from these other issues.

22 Another thing that was made very clear is

1 that we need to understand the opioids better so
2 that the treatment that we provide to pediatric
3 patients can be scientifically based. We use these
4 drugs, and we have derived fragmented experience,
5 which Dr. Hertz spoke about, but many believe that
6 the information available to inform best practice
7 is not really there in most cases.

8 PK data, safety data, and efficacy data are
9 things that people believe will help in informing
10 rational use of drugs going forward and in creating
11 new novel compounds for the treatment of pain.

12 Many people spoke about the need for a
13 balanced approach that does not reduce the option
14 for the use of opioids for patients that have a
15 recognized indication. And specifically, a group
16 such as palliative care, our oncology patients,
17 sickle cell patients, these patients have real pain
18 and they have pain for long periods of time. It
19 affects them physiologically and psychologically.
20 There are ethical and physical concerns associated
21 with this. We cannot make decisions -- or the
22 agency should not make decisions that forget these

1 groups who have chronic pain.

2 The safety concerns that were discussed
3 really relate to all groups of children across the
4 board. And Dr. McCann very elegantly spoke of
5 babies and where we start, and there is subsequent
6 discussion and disagreement about the granularity
7 of the data. Where do we begin in investigating
8 safety with opioids?

9 We need to define the current state of
10 safety in each individual developmental group, and
11 that would be, in my estimation, from the in utero
12 state to perhaps the mid-20s. We need to have that
13 continued discussion among ourselves.

14 There is a special case of treatment of pain
15 with opioids in the neonate, and it is an
16 underdeveloped science right now and needs to be
17 dealt with. Obviously getting information about
18 treatment of any of these patients, but especially
19 neonates, is going to require a large number of
20 patients. And many people have focused on the need
21 to use currently available networks, such as the
22 Oxford network, but other networks that are

1 available to us to implore them to help us derive
2 research, design, and gather data that would inform
3 the use of these drugs.

4 These neonates are not a rare group, and we
5 have said that the premature are exposed in utero
6 and in the neonatal intensive care unit through the
7 use of methadone post-operatively and after they
8 get out of the hospital if they're on ambulatory
9 methadone. So we've got a problem there.

10 In terms of what drugs to study, a comment,
11 a prescient comment I thought was to study drugs
12 that have safety and efficacy established in
13 adults, the safest drugs first, and that would not
14 be codeine, and that the inclusion criteria for
15 most of the studies -- for many of the
16 studies -- are so strict that they reduce the
17 number of patients that can be utilized to actually
18 derive data.

19 So those might need to be altered, and we
20 need maybe to think about study design in an
21 entirely different way, including using things like
22 PCA rescue and opportunistic trial design.

1 One of the major issues that we heard again
2 and again was the problem of having reasonable data
3 in order to assert what the state of safety is for
4 children around the country who are taking opioids.
5 Where is the data and how do we get it? How can we
6 help the FDA push along larger datasets. Are there
7 other datasets that are available to us now that we
8 are not seeing? Again, I'll say this might be one
9 of the biggest issues that we've heard about in the
10 last two days.

11 In addition to having the data, a comment
12 was made about where we start with defining the
13 data. And there may be the requirement for going
14 back to the beginning and defining some sort of
15 taxonomy of painful conditions prior to defining
16 risk and benefit of doing individual studies in
17 individual groups.

18 For large studies like this, a
19 public/private partnership might be in the best
20 interest of children's health, perhaps involving
21 the FDA with the NIH, the American Academy of
22 Pediatrics, International Anesthesia Research

1 Society, and the International Association for the
2 Study of Pain.

3 Those are the comments that I derived, the
4 larger comments that I derived. Anyone have any
5 other comments before we break?

6 (No response.)

7 DR. BROWN: If not, we're going to break
8 now, and we're going to come back at 11:00 and get
9 started again.

10 (Whereupon, at 10:45 a.m., a recess was
11 taken.)

12 DR. BROWN: Let's get back to our seats and
13 get started again. We still have quite a bit to
14 cover, and I'd like to get out of here by 2:00.

15 (Laughter.)

16 DR. BROWN: Just kidding.

17 We're going to question 2. We have had a
18 wide ranging discussion in question 1, in which
19 some of the issues in question two have been
20 discussed.

21 If it is the feeling of the group that we
22 need to completely go through question 2, we can do

1 so, or if there are individual comments that folks
2 have, in addition to those that relate to our
3 discussion in question 1, we will take that into
4 advisement, or we can go on to question 3.

5 So I'm going to read question 2 into the
6 record, and it is a discussion question. Clinical
7 trials ideally enroll the target population for the
8 study drug. Discuss the important factors that
9 clinicians should incorporate into their decision
10 to prescribe opioid analgesics in pediatric
11 patients, taking into consideration medical
12 conditions, safety, and other factors you believe
13 are important for proper patient selection.

14 Is that question clear to the panel?

15 DR. KAYE: Yes. Alan Kaye, LSU. I think I
16 made the comment about 20 minutes ago. One was, as
17 Dr. White had suggested, embedding and
18 communicating with IRB directors to see if we can
19 utilize existing study protocols vis a vis these
20 clinical trials.

21 The second comment I made was utilizing
22 pharmacy data to identify high prescribers in our

1 target populations of children and neonates, and
2 try to entice them through some sort of
3 communication program through a pre-created, very
4 simple protocol that incentivizes them through a
5 grant and provides support, because some of these
6 prescribers may be in a private setting and not in
7 traditional academic settings.

8 So I think those were my two comments, and
9 thank you for giving me the forum again.

10 DR. BROWN: Dr. Emala?

11 DR. NEVILLE: So at the risk of being
12 repetitive, I just wanted to comment that I'm not
13 sure that current clinical trials capture the
14 target population. And I would encourage sponsors
15 and the FDA to relook at inclusion/exclusion
16 criteria of the trials that are out there because
17 some of them are not accruable.

18 DR. BROWN: Dr. Emala?

19 DR. EMALA: Just a suggestion going forward
20 in clinical trials, particularly those that might
21 have a prospective component to them. Within the
22 field of opioid pharmacology, it's been mentioned

1 several times the diverse polymorphisms that can
2 affect drug responses, and at the very least, a
3 consideration for biobanking samples from patients
4 that this could be looked at in subsequent studies.
5 And some biological samples would be collected
6 anyway, it would be reasonable to have a biobank to
7 look at the impact of polymorphisms in these
8 groups.

9 DR. BROWN: Dr. Gupta?

10 DR. GUPTA: So as a pain doctor, one of the
11 things that I often see when I take care of
12 patients is -- or one of the concerns I have often
13 is when a patient gets their medication, leaves the
14 pharmacy, and being able to predict that they're
15 actually going to take the medication, as I've
16 prescribed, or they're going to actually take the
17 medication as they want.

18 One of the ways that I've seen in clinical
19 practice that's been very effective, and maybe of
20 value to study, is to really look at maybe a
21 screening tool, or some type of assessment after
22 the patient has initiated opioid therapy, to

1 determine if they understand how to take the
2 medication safely; if the provider has educated
3 them on the safe use of the medication,
4 particularly in pediatric patients; do the family
5 members understand when there's a problem, and what
6 they need to do.

7 I think some of those things are not really
8 addressed in clinical practice. Most of my
9 colleagues will not have those discussions on an
10 outpatient basis on whether or not these
11 medications are even being taken appropriately.
12 Parents and families leave the office not knowing
13 the correct way to dose these medications, and
14 that's where trouble can sometimes arise.

15 In addition, I think screening looking at
16 history of compliance of medications, medication
17 adherence, is there a history of aberrancy? Is
18 there a history of misuse or substance-use
19 disorders? And is there any history of analgesic
20 trials of non-opioids? Is there any history of
21 benefit with a trial of opioid therapy?

22 I think some of those screening assessments

1 that are done before the initiation of opioid
2 therapy has been very effective in determining
3 whether the patient will have a safe outcome. And
4 I think it would be of value to study in a
5 pediatric population, if a screening tool such as
6 that would be effective.

7 DR. BROWN: Dr. Havens?

8 DR. HAVENS: Thank you. I think the
9 question is well made, has been discussed at great
10 length, and I just want to be very supportive of
11 the FDA as they bring to bear the pressure that
12 they can bring, both on sponsors, as well as the
13 NIH, to be able to study these factors by age
14 group, in different clinical settings, by different
15 painful stimuli, to measure both the acute and
16 chronic benefits and long range outcomes, and to
17 show the support, at least for parts of the
18 committee, on their need to do that.

19 DR. BROWN: Dr. Lasky?

20 DR. LASKY: Thank you. I think yesterday,
21 in the overview about prescribing, we heard about
22 dental prescribing of opioid analgesics. So that

1 there were 94,000 prescriptions for
2 immediate-release opioids in children aged 2 to 6,
3 and 709,000 prescriptions in children 7 to 16.

4 There's a lot we don't know about the
5 prescribing. We weren't given information about
6 the indications for prescriptions. But it seems to
7 me this is a patient pool and a setting that could
8 be used for clinical trials, that could possibly
9 answer some questions that we might want to have
10 answered in terms of labeling.

11 We would of course have to learn about the
12 leading indications for the opioid use in dental
13 practice; find out which medications are used;
14 think about the feasibility and ethical concerns
15 about conducting clinical trials in dental
16 practices, focusing on the drugs; and whether we
17 could learn about efficacy and safety in a way that
18 would be relevant to our labeling concerns.

19 I think it would be a very good opportunity
20 also to learn about their prescribing and whether
21 the prescribing is contributing to some of the
22 other kinds of issues we've been discussing in the

1 past day and today. So I'm recommending that we
2 explore clinical trials in dental settings.

3 DR. BROWN: Dr. Nelson?

4 DR. NELSON: From the patient's perspective,
5 I just wanted to probably ditto some of what has
6 already been said. I have a pharmacy at my house
7 of old medications that I can't rid of. And I
8 asked the pharmacist how to get rid of them, a
9 church may have a drive where you can throw them
10 away. I missed that day, so I have lots of old
11 medication. So that would be one thing for them to
12 consider.

13 The other, I think Dr. Gupta spoke to this
14 about patient education. I have been in charge of
15 my daughter's medication and teaching her how to
16 take her own medication. We don't take
17 the -- we're instructed not to take these products
18 unless I call the doctor. So if I feel that her
19 pain is getting out of control, we call. They
20 determine whether we're to take the immediate
21 release or the extended release. We already have
22 prescriptions for those things.

1 Then we have a follow-up nurse. Their team
2 has a nurse that calls me a couple of days later to
3 ask how she's doing, whether she's taking the
4 extended release or the immediate release. And I
5 find that to be a good system. I mean I understand
6 that everyone is not compliant, but just a few
7 thoughts there about the safety.

8 DR. BROWN: Dr. Kaye?

9 (Dr. Kaye gestures no question.)

10 DR. BROWN: Dr. Bateman?

11 DR. BATEMAN: So it strikes me that we
12 really need more data to define the clinical
13 situations where opioids are even needed for
14 children. We saw the utilization data yesterday
15 from IMS, and as one of the previous speakers
16 alluded to, dentists account for 20 percent of the
17 prescribing of opioids in kids aged 2 to 6, and
18 30 percent of the opioids in kids 7 to 16.

19 There's at least some data to suggest that
20 NSAIDs are more effective for most forms of dental
21 pain than opioids. So I think stepping back and
22 even just looking at when these medications, given

1 their considerable risks, are absolutely indicated
2 will be important.

3 DR. BROWN: Dr. Ruha?

4 DR. RUHA: Yes. Michelle Ruha. I was just
5 going to say that definitely, I think it would be
6 wonderful if we could recommend to all physicians
7 to limit the number of opioids prescribed for all
8 the acute painful conditions, such as dental
9 procedures, to think about how long the pain, the
10 acute pain is anticipated to last. Because in many
11 of the diagnoses, I think that adolescents or
12 children are being prescribed opioids for -- the
13 painful conditions should probably be improving
14 dramatically over a few days, yet I think a lot of
15 them are getting prescriptions to last sometimes
16 30 pills at minimum.

17 So there's a lot of leftover, which is why
18 then they're able to go out and sell to friends and
19 families are able to divert them. So perhaps with
20 the prescribing, to think about what's the
21 anticipated length of time and only give that
22 amount, and then a reassessment is necessary to get

1 more.

2 DR. BROWN: Given that the question is to
3 discuss the important factors that clinicians
4 should incorporate into their decision to prescribe
5 opioid analgesics in pediatric patients, taking
6 into consideration medical conditions, safety and
7 other factors you believe are important for proper
8 patient selection, what I have heard over this last
9 few minutes is that there are many factors, not the
10 least of which are the educational attainment of
11 the patient, the patient's history of drug use,
12 which I would also include in that history of
13 family misuse of drugs.

14 One thing that we haven't discussed is a
15 history of mental illness in individual patients.
16 Certainly for our patients, the developmental level
17 of the patients.

18 Then pursuant to the discussion of the use
19 of opioids for post-dental surgery, of course we
20 would have to give consideration to each individual
21 surgical or medical condition in determining what
22 factor would be most appropriate.

1 Can we move on to question number 3?

2 Question number 3 is, studies of immediate-release
3 opioid analgesics are generally conducted in
4 patients with acute painful conditions, including
5 post-operative pain, as well as traumatic or other
6 painful conditions, that require opioid analgesia
7 and are expected to be of relatively short
8 duration.

9 Studies of extended-release opioid
10 analgesics are generally conducted in patients
11 expected to require opioid treatment for at least
12 two weeks, who have pain severe enough to require
13 an opioid, such as cancer pain, post-surgical pain
14 for major procedures, sickle-cell pain, and other
15 medical conditions.

16 Pediatric patients in studies of
17 extended-release opioids are required to have
18 received opioids for a period of time prior to
19 entering the study to assure that they tolerate the
20 lowest available strength of the extended-release
21 opioid.

22 The agency is asking the committee to

1 discuss incorporating the factors identified in
2 discussion number 2 into the pediatric populations
3 selected for the study of opioid analgesics. And
4 I'm going to ask Dr. Hertz if she could clarify
5 this question for us.

6 DR. HERTZ: Apparently, I'm having a
7 difficult time. The idea was, if we were going to
8 get specific factors about patient selection, about
9 safety, from the prior questions in terms of target
10 populations, that sort of thing, how to incorporate
11 that into these different studies for the IRs and
12 the ERs.

13 I guess, basically, if you were thinking
14 about drugs, the opioid analgesics -- and if you've
15 already said this to some extent with other
16 settings -- in terms of these studies, how would
17 you define the appropriate populations for these
18 different programs, for IRs and ERs?

19 DR. FIELDS: And I think folks have
20 mentioned that perhaps the inclusion/exclusion
21 criteria should be changed from what we're
22 currently doing, and this would be a good time to

1 bring that up.

2 DR. BROWN: Comments? Dr. Patrick?

3 DR. PATRICK: Just a quick question about
4 drug classes and whether or not maintenance
5 medicines -- we haven't spoken a lot about that,
6 and perhaps Dr. Levy could comment too on whether
7 or not -- let's say that we had a 14-year-old under
8 the indication for buprenorphine, goes to 16 I
9 think, so whether or not that should be a part of
10 the conversation as well.

11 DR. HERTZ: If we have a lot of extra time
12 and you have some additional thoughts about the
13 opioids used as part of medication-assisted
14 treatment for opioid use disorder, fine, but we're
15 really trying to get at the analgesic piece right
16 now.

17 DR. BROWN: Dr. Walco?

18 DR. WALCO: I think there are a couple of
19 issues that come into play here that we heard
20 discussed yesterday. Most of the time when there
21 is a study to be done in a pediatric population,
22 the drug has indications for various pain problems

1 in adults, and then the first effort often then
2 tries to parallel that in pediatrics.

3 So the first question would be, is there
4 really a parallel? So if it's a drug that has
5 focused on neuropathic pain syndromes in adults,
6 and now you want to do the study in children, the
7 question is, are there really viable models? Is
8 that a reasonable downward extension?

9 The second is that I think we've come to a
10 point where we can be a bit more focused. I'm
11 tempted to joke a little bit and say I'm a delegate
12 from the great State of Washington, where we've led
13 the charge in trying to curb opioids, and I was
14 asked to contribute to the guidelines from the
15 state on when one would use opioids for more
16 chronic therapy.

17 I think the first critical question you need
18 to ask is, is the pain condition that you're
19 looking at one that is known to respond to opioid
20 therapy? Does it have nociceptive bases, for
21 example, as opposed to neuropathic or more visceral
22 or central sensitization? If the answer to that

1 question is no, I think it doesn't make sense to
2 proceed, so I think that would be one critical
3 question, is really narrowing down those inclusion
4 criteria.

5 The second kind of gets at the issue you're
6 raising here about timing. And I think the
7 critical next step if you're going to use opioids
8 for any extended period is to define an endpoint.
9 When will you no longer use opioids? What needs to
10 happen in order to discontinue that therapy?

11 I think that if you're looking at the
12 pediatric population and who is using these drugs
13 for greater than two weeks or four weeks, whatever
14 you're going to define, you're going to probably
15 end up with relatively small numbers.

16 So I think thinking about the whole timing
17 thing is critical in terms of really understanding
18 the populations where extended-release drugs are
19 indicated. And as was shown in the OxyContin
20 trial, you end up with relatively few conditions
21 and relatively small numbers of patients.

22 So I guess those would be the two starting

1 points. The obvious third issue that we put in the
2 state guidelines is that if you are thinking about
3 using opioids on anything beyond an acute basis,
4 it's imperative to get a screening for abuse
5 potential. And the recommendation there is by
6 somebody who is trained to do that, not just a
7 screening instrument, not just asking a few
8 questions about risk factors, but a more formal
9 assessment by somebody, such as Dr. Levy or that
10 equivalent, if you're going to go in that
11 direction.

12 DR. BROWN: Dr. Havens?

13 DR. HAVENS: Thank you. Peter Havens. I
14 think one of the issues here is that you're talking
15 about treating chronic pain, and as such, you would
16 need to make sure that opioid use was in the
17 context of the DHHS National Pain Strategy, which
18 specifically identifies chronic pain as a
19 bio-psychosocial problem that requires a broader
20 group to treat it.

21 While this is an expensive undertaking, it
22 suggests that opioid use is an adjunct to other

1 non-opioid measures. And if we're going to
2 recommend treatments, we should recommend
3 treatments that meet guidelines promulgated by
4 other federal committees.

5 DR. BROWN: Dr. Neville?

6 DR. NEVILLE: So just a comment specifically
7 on the second part of question 3, and I don't
8 necessarily think I have the most brilliant answer.

9 I understand why it's designed that way, but
10 what has been problematic is the period of time for
11 which patients have had to have been on opiates
12 plus the expectation of at least two weeks. And a
13 lot of these patients go home. I understand the
14 safety piece of that, but I think it might be worth
15 reexamining that, because we learned yesterday that
16 sometimes even these long acting opioids are not
17 used for that duration of time in major surgeries,
18 especially when you combine them with the immediate
19 post-op period of IV.

20 So I think we need to, again, look at
21 balance and safety with inclusion criteria so we
22 can accrue to these trials. And maybe, we've

1 talked a lot yesterday, today, about current use
2 versus how to design a trial. I mean, we've heard
3 survey information, but maybe that can be used to
4 inform this portion of the trial design.

5 DR. BROWN: Dr. White?

6 DR. WHITE: Thank you. Michael White, New
7 Orleans. I'm going to be a heretic. That's not
8 unusual. It seems to me that understanding the
9 difference between intermediate release and the
10 extended release in children might pose a very
11 different question than it does in adults. And it
12 looks like one of the major areas of utilization
13 for any opioids is among orthopedic surgeons. And
14 our surgeon who was here the other day is a surgeon
15 at one of the Shriners hospitals, and there are
16 lots of orthopedic procedures done there.

17 It's a fairly predictable population. You
18 know what the procedures are. You know when
19 they're going to do the procedures. It seems like
20 that's an accessible population of subjects for
21 trials. And other orthopedic hospitals for
22 children, or major orthopedic centers for children

1 might be approached as well.

2 It seems like it would be worthwhile doing a
3 trial of opioids versus just non-steroidals in
4 children with a bail out if the child is not doing
5 well. It also might be worthwhile, even for
6 shorter than two week periods of time, to look at
7 the efficacy of an extended release versus an
8 intermediate release to see if you get better pain
9 control for even short periods of time using an
10 extended-release option.

11 But that might be one way to approach
12 getting enough subjects, which we've heard is a bit
13 of a problem, for any opioid studies in children.
14 And it might give you an opportunity to use a
15 basically fixed population of disease processes
16 that might give you better control over your
17 outcomes, or expectations.

18 DR. BROWN: Dr. Hoehn?

19 DR. HOEHN: Sarah Hoehn. To follow up with
20 Dr. Neville and Dr. White just mentioned, I
21 certainly agree that we should think about narcotic
22 equivalent, especially if we want to study the

1 extended-release population. I love the idea of
2 trying to get the surgeons involved, either through
3 the Shriners hospitals, or the other thought would
4 be to look at some of our adolescent trauma
5 patients that come in and are on very high dose IV
6 narcotics.

7 Lots of times the trauma surgeons
8 specifically want them on extended release for the
9 same reasons we heard from the orthopedic surgeon
10 yesterday in terms of mobility and things like
11 that. So I don't know if there's some way to sort
12 of look at narcotic equivalent, especially in the
13 spinal fusion or in the trauma patients, and then
14 look at both non-steroidals, looking at the use of
15 earlier scheduled Toradol, and looking at
16 extended-release narcotics.

17 None of those patients would fulfill the
18 requirement of at least two weeks, but they're a
19 relatively healthy, robust population that's having
20 a lot of pain, and we might be able to get a lot of
21 information from them.

22 DR. BROWN: For our FDA colleagues, we need

1 some direction here because we're getting well off
2 of what the question actually asks. And I need to
3 get some counsel about what more you would like to
4 hear about.

5 We talked when we were discussing the first
6 question, and this gets to the factors that would
7 derive from getting pediatric patients into studies
8 of opioid analgesics. We had talked about the use
9 of opportunistic trial designs and the positives
10 and the negatives of that.

11 One thing that we've discussed the fact that
12 it has been discussed before but not really
13 discussed it, is the utilization of PCA rescue as
14 an important part of trial design relevant to not
15 forcing us to have a placebo -controlled group in
16 the design of trials.

17 Are we on the right track?

18 DR. HERTZ: Yes. I mean, this is
19 interesting just to hear the thoughts. So if this
20 will help a little bit in terms of the discussion.
21 When we look at these studies in all of the
22 pediatric ranges, if I target first the acute pain

1 IR studies, typically what we use in terms of a
2 study design is an add-on design to standard of
3 care.

4 Analgesic studies are challenging because we
5 have studies that fail with known analgesics, and
6 when you look at study design, enrollment, all of
7 that, it's hard to figure out why. So we have a
8 general standard for analgesics that we require
9 some demonstration of superiority to a comparator,
10 as opposed to a non-inferiority study, because in a
11 non-inferiority study, showing that you're not
12 substantially different from your comparator means
13 both products work or both products don't work. So
14 we need some type of assay sensitivity.

15 In the IR products, it's a little bit easier
16 because typically they'll be on a standard of care.
17 We'll add the study drug on a regular schedule and
18 placebo, and then look at the reduction in standard
19 of care or rescue.

20 If the standard of care is PCA or another
21 oral, or what have you, that all typically can
22 work, and it doesn't create an opportunity for the

1 child to have more pain than they would have
2 experienced with standard of care.

3 For the older patients who have studies of
4 oral products, IRs or ERs, in the perioperative
5 setting where it might be a little bit longer
6 exposure, we try to do a similar type of design.

7 A challenge of this setting is what can you
8 add on safely to existing therapy. So it depends
9 in part on what standard of care is. So some of
10 these children may already be getting an NSAID.
11 Some of them may be getting another opioid.

12 I think what I'm hearing is, at least in the
13 setting of the second part of the question, some
14 alternative study questions about the use of
15 opioids. And that, you know, is not the direct
16 question that we're asking, but it's still a very
17 useful set of comments.

18 I think, yes, within the constraints of what
19 we're able to do in children with regard to study
20 design, I think that the kind of comments we're
21 getting are helpful. And in terms of building on
22 the earlier questions, I think we already touched

1 on a lot of those factors with some of the earlier
2 discussion. The question responses aren't quite as
3 parsed as we envisioned them, so we're getting, I
4 think, a picture over the course of the
5 conversation.

6 DR. BROWN: Dr. Lasky?

7 DR. LASKY: So I'm not sure. I had a
8 concern, and I'm not exactly sure where it fits
9 into the sequence of questions. But yesterday when
10 we heard about the -- again, I'm going back to the
11 presentations by Dr. Pham. I'm an epidemiologist,
12 so that's what I kind of gravitate to. But it was
13 all in the outpatient setting, and most of our
14 discussion I think is going to the inpatient
15 setting. And there are inpatient databases with
16 information about opioid use, so that's one set of
17 questions to explore those databases further.

18 But there is another set of issues that
19 sometimes when we go to the inpatient setting,
20 we're going from the disease condition, saying
21 these are the kids that we'd like to study. But
22 there are kids in the inpatient setting who are

1 getting opioids, and they're not necessarily the
2 same kids that this group of people here think
3 should be getting opioids.

4 I just wanted to bring some information to
5 the attention of everyone that a large database
6 that is not a nationally representative sample, but
7 did look at, for example, morphine use in the
8 hospital, estimated that 6.3 percent of all
9 children, all pediatric hospitalizations in 2008
10 received morphine during their hospital stay. And
11 that would translate into 476,000 hospitalizations.
12 This isn't the opioid we're concerned with, but
13 there is information in these databases. It's
14 possible to drill deeper.

15 There is an issue that someone else brought
16 up that this kind of secondary analysis needs to be
17 conducted by someone, and funded. However, it's
18 very useful in terms of thinking through the
19 planning for clinical trials and picking
20 populations that may not be the top priority from a
21 clinical point of view, but may be feasible in
22 terms of getting the labeling done.

1 So in looking at the population that had
2 morphine use, any morphine use during the hospital
3 stay, this is not talking about what other drugs
4 they had, how many doses, what the dose was, or how
5 many days they received it. But the top three
6 discharge diagnoses, which is again not necessarily
7 the indication for the prescribing, were
8 appendicitis, fractures, and diseases of the blood
9 and blood-forming organs, in children 5 to 11.

10 In children 12 to 17, the top three
11 diagnoses in this group were appendicitis,
12 fractures, and surprisingly, something we haven't
13 mentioned, normal delivery and other indications
14 for care in pregnancy.

15 The point is that taking a look at this kind
16 of database can help flesh out some of the
17 information to inform a discussion like we're
18 having here, that there needs to be back and forth
19 between the clinicians asking questions about the
20 patient groups, and the data feeding into the
21 discussion, saying no, we don't necessarily have
22 large numbers there, but we have large numbers

1 here, and perhaps we could at least answer
2 questions A, B and C in this way.

3 So I've been concerned about this issue,
4 especially in reading the briefing document, the
5 need to look at inpatient databases. I've been
6 hearing people talk about databases, and I probably
7 will mention this later in the day, the
8 opportunities to analyze databases for
9 observational data.

10 But a lot of children are treated with
11 opioids in the hospital, and they may not match the
12 patient groups that the clinicians would like to
13 see studied. But they do indicate where the
14 medications are being used and where some studies
15 might be feasible. And I'll leave it at that for
16 right now.

17 DR. BROWN: Dr. Wade?

18 DR. WADE: Thank you. My comment's been
19 resolved and stated.

20 DR. BROWN: Dr. White?

21 DR. WHITE: Apparently I derailed in the
22 last discussion. But the area of concern that was

1 brought up over and over again this morning is
2 neonatal use of opioids, which may or may not
3 necessarily be related to pain as much as it might
4 be related to neonatal addiction. And that's
5 probably best addressed through the pediatric
6 network, groups like the Oxford study and such, as
7 a source of subjects.

8 But I don't really know what you would do
9 for long-term outcomes in that. I just don't know
10 how you're going to be able to sort out endpoints
11 or information to help you make decisions on when
12 to start, when to stop. Is one opioid better than
13 another? Those are really going to be tough
14 questions to sort out. Then the other group, as
15 noted, are those that are iatrogenically addicted
16 to opioids, and how do you manage that?

17 Are opiates even necessary in the neonate?
18 Are there other options? Not opioids, non-opioid
19 drugs that would serve the purpose as effectively
20 would be another way that we should be addressing
21 this issue I guess. And I don't know how to go
22 there. I'm not a neonatologist. I'm not that

1 familiar with pain control in neonates, but those
2 are questions that someone naïve might look at and
3 go, well, why are we even using opiates when we put
4 the kid on pump? Maybe we just need sedation.

5 Thank you.

6 DR. BROWN: Thank you, Dr. White.

7 Dr. Patrick?

8 DR. PATRICK: Just a quick comment. So as
9 far as like the relative amount, so far more
10 infants have drug withdrawal from antenatal
11 exposure than infants that have iatrogenic
12 exposure. It's probably in some of our work,
13 probably around 1,000 of the 27,000 are from
14 iatrogenic exposure, and they are a different
15 population.

16 But I would say this, that as far as that,
17 yes, it's a complex thing to think about long-term
18 outcomes, but we have done it within the neonatal
19 network. And I would say that this is no more
20 complex than the heterogeneity among very low birth
21 weight infants. So just because it's difficult
22 doesn't mean it's not something that we should do.

1 I think it's important, and certainly there is some
2 infrastructure to begin to ask those questions
3 through, the NICHD funded neonatal network. But I
4 think it's difficult, there's heterogeneity, but I
5 think it's worthwhile.

6 DR. WHITE: I didn't mean to imply that it
7 wasn't worthwhile.

8 DR. PATRICK: Thank you, sir.

9 DR. BROWN: Any other comments?

10 (No response.)

11 DR. BROWN: We're going to break for lunch
12 here. But before we break, I'm going to very
13 briefly try to define what it is that we have just
14 spoken about. The fact of incorporating children
15 into research design, and has been demonstrated to
16 us over the last two days, it's difficult and will
17 almost certainly continue to be difficult, but must
18 be considered.

19 Issues that must be utilized in dealing with
20 issues about design include safety issues that
21 we've touched on this morning. These safety issues
22 include toxicological issues, acute respiratory

1 depression, as well as the impact of chronic opioid
2 use on the developing brain.

3 In addition, does the clinical condition
4 even respond to opioids? Could opioids be used as
5 a third-line drug? Is the trial designed in a way
6 that will be relevant to a clinical condition that
7 children actually have rather than a shotgun
8 approach to design? And last, whether or not it is
9 necessary in each individual patient to screen for
10 risk factors relevant to the use of opioids, not
11 only in the patient, but if it's an ambulatory
12 patient, in the patient's family.

13 We're going to break for lunch. I think
14 that we're going to come back at 12:45. Please
15 take any personal belongings that you want with you
16 at this time. And remember there should be no
17 discussion of the meeting during lunch amongst
18 yourselves, with the press, or with any member of
19 the audience. See you at 12:45.

20 (Whereupon, at 11:43 a.m., a lunch recess
21 was taken.)

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

(12:45 p.m.)

DR. BROWN: So we're going to continue with the questions to the committee and our discussions. And question number 4, as you can see, is extrapolation of efficacy from adults to pediatric patients down to age 2 is utilized in the development of opioid analgesics.

We have had situations where the PK data in pediatric patients was not similar to adults, as would have been expected. In this situation, would it be appropriate to identify a safe starting dose that would be titrated to effect, or should efficacy be evaluated?

Dr. Hertz?

DR. HERTZ: Yes. I'd like to provide a little background for this, because this question kind of feels like it's a little bit unrelated to a lot of what's gone on. This is a little bit related to some of the clarifying discussion that occurred yesterday with regard to a few comments.

1 But basically, when we initially get a PK
2 study, PK and safety for an opioid in a population
3 that we would have otherwise thought we could
4 extrapolate efficacy, that's based on an
5 expectation that there will be a similar PK/PD
6 response, and that the exposure in children will be
7 similar to the exposure in adults.

8 But what we have found, at least in one
9 case, was that the expected exposure, based on the
10 modeling and looking at guidelines, that the final
11 dose selection for the clinical protocol resulted
12 in substantially less exposure to the opioid, and
13 then we were left wondering what that meant for
14 extrapolation.

15 So the question that we have basically is,
16 when we think about extrapolation in a broad sense,
17 with the opioid products, given that they're
18 typically titrated to effect based on both efficacy
19 and side effects, is there a particular goal for
20 establishing an appropriate starting dose; and how
21 should that be considered with regard to the
22 typical expectation that exposure should be the

1 same in the context of extrapolation? Does it mean
2 the study should be redone? Is it enough to
3 identify a safe starting dose?

4 In this particular case, we lacked certain
5 other information that would have helped to
6 identify a little bit more what that clinical
7 situation means. But is it okay to see a smaller
8 exposure than expected, and then rely on other data
9 to supplement our understanding? So for instance,
10 the use of rescue medication and/or clinical
11 ratings of pain and safety, given that these are
12 typically open label studies?

13 So that's a little bit of the baggage that's
14 sort of behind this question.

15 DR. BROWN: Comments? Dr. Kibbe?

16 DR. KIBBE: I was waiting for these
17 questions. These are my kind of questions. First,
18 we all recognize that pain is a symptom not a
19 disease; that everybody is talking about different
20 patient populations, don't forget this one, don't
21 forget that one, don't forget this one. Well guess
22 what, we're talking about a common symptom, not a

1 common disease.

2 As a result, in order to have any
3 information that's useful, we have to generate a
4 matrix of information, one where across the top of
5 the matrix we have different diseases, and down the
6 side we have different age groups. And then we
7 need to develop a guideline or a number that can be
8 used by the clinician as a starting point.

9 We know -- maybe you don't know, but we know
10 that across mammals, if you reach the same minimum
11 effective concentration of a drug, you'll expect to
12 get the same physiological and pharmacological
13 effect in full-grown animals, so that the levels
14 that you need to give relief for blood pressure in
15 a human, is the same level that you need if you
16 have a hypertensive dog. The difference is how you
17 give them the drug and how do you get that much in,
18 and when you deal with ruminants, that's a whole
19 other problem.

20 What we have here is that we have a
21 developmental time frame where the enzymatic load
22 changes over time. And we all know that neonates

1 and preemies and what have you have no ability to
2 metabolize relative to their older compatriots. So
3 what we need to do is establish some kind of a
4 descending or ascending, depending on the way you
5 want to look at it, a way of evaluating the opioid
6 in a given age group to see if there is a trend,
7 and I talked about that yesterday.

8 Here's the study. Okay? Whenever there is
9 a group of patients that are being treated by
10 someone with opioids that are in a same cadre in
11 terms of the disease -- so if our orthopods have
12 5 kids who are in the range of 12 to 14 with broken
13 arms, bing.

14 What they do is they start out with a low
15 dose and they ratchet it up until the patient is
16 able to say that they are no longer in pain, and
17 then you wait. And when the patient says the pain
18 has come back, you take one blood sample, and you
19 keep dosing them. And that one blood sample gives
20 you an estimate of the minimum effective
21 concentration in that group of pediatric patients
22 with that condition, and that goes into the matrix.

1 Just like when we built the periodic table,
2 we didn't know all the cells when we start, but we
3 start filling them in. And once we start getting
4 them filled in -- and each one of these mini
5 studies can be done in a clinic somewhere or with a
6 small investment, if you will, in energy over and
7 above the therapy for a patient.

8 We start filling it in; we'll see trend
9 lines. We'll see trends even if it's just three
10 dimensional physical platform where you can look at
11 how age groups handle the drug when suffering this
12 condition, and see whether or not there is
13 consistency across conditions or across age groups.

14 If you do that, and you start with patients
15 who can effectively report to you that they're in
16 pain or not in pain, you'll get numbers for peds, I
17 guess from what, 7 or 8 years old on up. And if
18 there is some kind of an internal trend, then you
19 only have to match it with the internal trends that
20 we know about in terms of enzymatic development for
21 an enzyme that deals with that opioid.

22 All right. Now you can start to extrapolate

1 back down to patients that you can't ask are they
2 in pain or not. And with that information, you can
3 start determining a starting dose and a dose that
4 would be ideal for the pain in that condition. So
5 if you have a 1-year-old with a broken arm, and
6 you've done these studies with broken arms and
7 broken legs down from say 16 to about 7, and you
8 see the trend, and you know you're using an opioid
9 that has cytochrome P450 enzymatic metabolism, then
10 you've got a way to do that.

11 Now that takes a lot of time, and it's a lot
12 of rudimentary experimentation. But in the end,
13 you'll have a periodic table, if you will, for
14 where to start when you start giving therapy.

15 Now, this is all compounded by the fact that
16 every individual has a different level of
17 sensitivity to pain, and a different level of
18 sensitivity to the opioid. But what we're going to
19 end up with is a starting point, and from then on,
20 every clinician dealing with their individual
21 patient will have to make clinical judgments about
22 how much more to add to get to where they want to

1 get in terms of relief of pain. But we can't, I
2 don't think, in any rational way, come up with an
3 answer for every patient you'll ever see by looking
4 at population data.

5 So that's my 4 cents worth for 4, 5, and 6,
6 and good luck.

7 DR. BROWN: Any response?

8 DR. HIGGINS: That's excellent.

9 UNIDENTIFIED MALE: Sorry. Could you repeat
10 that?

11 (Laughter.)

12 DR. KIBBE: Yes, I could, but it's okay.

13 DR. BROWN: But how do you know where to
14 start?

15 DR. KIBBE: Okay, so in each one of the
16 cells, when you undertake that cell -- the
17 gentlemen who was here with his orthopedic friends,
18 they have to say okay, what have we done in the
19 past? How have we treated these people in the
20 past? And start there, and do that one simple
21 sequence where they get to the point where the
22 patient is free of pain, and then tells you that

1 the pain has started again.

2 DR. BROWN: So, Dr. Kibbe, in terms of this
3 question, that would be in the first part of the
4 question, appropriate to identify a safe starting
5 dose. Is that what you're saying, that first we
6 identify a safe starting dose?

7 DR. KIBBE: What I'm saying is that most
8 clinicians already have that in mind. If they've
9 used opioids before, they have a sense of what they
10 like to use and why they like to use it. So that's
11 a good place for them to start, but what they don't
12 have is a mathematical reason why that is
13 functional.

14 They can get that with one blood sample.
15 And if they do it in 5, 8, 10 individuals, if they
16 can identify the minimum effective concentration
17 for that opioid in that subclass -- and we can't do
18 it -- you can't have a group as broad as from 7 to
19 16. You have to have smaller age ranges to be able
20 to map back on it.

21 DR. BROWN: Well, once again, I'm going to
22 ask, but where do you start because if you start at

1 age 7 -- and we heard pretty convincing data
2 yesterday about the overwhelming changes in the
3 metabolism of these drugs in younger children over
4 time. So how are we going to extrapolate from a
5 7-year-old to a 2-year-old or a 1-year-old?

6 DR. KIBBE: So there's no perfect answer for
7 everything. But because you'll have patients from
8 7 years on up who can explain to you when they
9 think they're in pain or when they feel pain, and
10 this pain is so subjective, you can start them with
11 a dose, have the pain go away, and find out when
12 the pain comes back. And you can then establish
13 the minimum effective concentration in that
14 patient, with that condition, with that drug. And
15 if you do it in increments of say 3 years, 7 to 10,
16 10 to 13, and so on, you'll have a sequence of
17 minimum effective concentrations across the range.

18 Now you have to go back to an even more
19 complicated thing, which is how quickly do they
20 develop the enzymes that handle that particular
21 opioid? I think we had some discussion of that
22 before. And that should be a background

1 information or whatever you have.

2 So now you know, at 7, that the average
3 pediatric patient is going to be 60 percent of an
4 adult in terms of enzymatic ability, and 13, and so
5 on and so forth. And now you've got your trend
6 line, and now you have to extrapolate, taking into
7 account the rate at which those enzymes develop,
8 and that gets you back.

9 Now, as we all know with statistics, the
10 further away you get from the data you have, the
11 broader the error. So it's still going to be very
12 difficult to get a tight estimate for the zero to
13 1, but you can do better than you could if you
14 tried to get them to explain to you whether they're
15 in pain or not. And at least you can have a
16 starting place and try to use your clinical
17 evaluation of the patient to know whether you have
18 to ratchet up or not. So at least you've got what
19 I think is the beginnings of a periodic table.

20 DR. BROWN: So from what I can discern, what
21 you're really providing us here is a combination of
22 number 1 and number 2 here, where that you're

1 identifying your safe starting dose, and to some
2 extent, getting at the issue of efficacy with some
3 extrapolation along the way.

4 DR. KIBBE: Right.

5 DR. BROWN: Would anybody else like to
6 comment on that? Dr. Flick?

7 DR. FLICK: I love the idea. It sounds
8 elegant. I do see one problem. You said 8 or 10
9 patients. I think it's going to be 800 patients
10 because there's enormous variation, not only in the
11 methodology, but in the pathology.

12 So if you take one child with scoliosis,
13 there is enormous variation in the children who are
14 having that pain sensitivity, ability to report
15 pain. So all these things introduce a lot of
16 variation in the population, which makes the sample
17 size grow and grow and grow. So although I think
18 it's great, it's probably not going to be 8 or 10
19 patients.

20 DR. BROWN: Dr. Walco?

21 DR. WALCO: I love the creativity. And the
22 \$50 million question that I think one would have if

1 I follow your reasoning is you're going to start
2 with children who can verbalize when they're in
3 pain, and then start to work your way back down to
4 younger and younger ages.

5 The problems that I see with the younger and
6 younger ages, comma, which is where we really need
7 the data the most, is that, number one, you're
8 going to lose that reliability of knowing when
9 they're in more pain; and number two, the
10 variability between kids at different ages is much
11 greater. So you're going to have a very, very
12 heterogeneous group on the exact parameters that
13 are being studied because of developmental issues.

14 So I love your idea for a start, and then
15 the challenge is, once you get below 2, and below
16 6 months in particular, I think it's going to get
17 pretty dicey, unless I'm missing something from
18 what you've described, Art.

19 DR. KIBBE: Well, it's research, it's not
20 testing. So with research you never know for sure
21 what you're going to get. If we get lucky and
22 there is a trend in MEC that matches the trend in

1 the metabolism rates that are present in the
2 population of pediatric or children of that age
3 group, as you move through the ages, then you're
4 more reliably predicting than you are without that.
5 But I don't know that until we actually do it.

6 But the least we can do is get a lot of help
7 for all the clinicians who are dealing with
8 pediatric patients between 7 and 14 as a place to
9 start and a way to look for the minimum effective
10 concentration of that drug in those people.

11 The study that I'm proposing is huge in a
12 lot of respects, but straightforward so that it
13 could be carried out at all sorts of clinics on all
14 sorts of sets, subsets, of the people with pain.

15 DR. BROWN: Dr. Ruha?

16 DR. RUHA: Just another idea to gather data.
17 Obviously, children are started on opioids all the
18 time, and presumably most of the time the dose that
19 is used is safe.

20 So although it wouldn't be as nice as
21 prospective data, perhaps another idea would be to
22 conduct retrospective studies at major pediatric

1 centers, looking at children who were initiated on
2 opioids, whether in the emergency department, post-
3 surgery, opioid-naive children who were giving
4 initial starting dose; do a retrospective study
5 looking at whether they had respiratory depression
6 following it, needed naloxone reversal, and whether
7 they had effective pain relief.

8 There's certainly limitations with
9 retrospective, but it might be more feasible to
10 rapidly identify safe starting doses that can be
11 recommended based on previous experience.

12 DR. BROWN: Dr. Cnaan?

13 DR. CNAAN: So this sounds like a combined
14 great plan, start with the literature to
15 identify -- or try to start, and then go from there
16 with this somewhat grand plan.

17 The dosing itself, by the time you're making
18 it to such fairly narrow age range, there's still
19 going to be a large variability in size. So there
20 comes the question of dosing per weight, per body
21 surface area, per ideal body weight. The dosing
22 itself I think is a question that's important for

1 the base study within that framework.

2 The other thing is, as you said or somebody
3 else said, yes, age 7, 8 is the age that they can
4 do these various pain scales in the phases and all
5 of that, and below that it becomes unreliable. But
6 you can go a little lower in age because even a
7 4 year-old can tell you if they're hurting or not.
8 They might not be very reliable on the pain scale,
9 but on the yes/no question of an effective dose, it
10 might still work, and therefore the extrapolation
11 becomes a little bit less.

12 DR. BROWN: Dr. Maldonado?

13 DR. MALDONADO: Sam Maldonado from J&J.
14 After this day and a half of conversations, I have
15 been trying to figure out how would I develop a
16 drug for this symptom or condition. And I'm still
17 puzzled because a lot of the comments is that we
18 don't even know the condition itself. Really, the
19 comments of Dr. Turer this morning resonate with
20 me.

21 We need to have a taxonomy of the disease,
22 or the condition. This is not a single entity;

1 it's many entities, some that we cannot even
2 diagnose in the newborn period. Or even if people
3 may argue that they can diagnose it because of
4 heart rate or because saturation, are those
5 surrogate markers that regulators will accept?
6 Maybe not, maybe yes. I don't know.

7 Then all of these little boxes that we will
8 be creating, as Dr. Kibbe said, all of these cells
9 need to be tested. So even before we start
10 studying drugs, we probably need to study pain.

11 DR. BROWN: Dr. Havens?

12 DR. HAVENS: Thank you. So the first
13 challenge, given by the question, is would it be
14 appropriate to identify a safe starting dose?
15 Presumably you would choose a dose that would give
16 you the PK target that you'd gotten in adults.

17 Is that accurate? So you do a study in
18 adults. You show that this dose works. You get a
19 blood level that is the 50th percentile, whatever
20 you got with that adult dose, and so you get an
21 adult exposure, which works in adults.

22 So is this a question about how to scale

1 from the adult starting dose to a starting dose in
2 younger children? Because that's a dramatically
3 different question than what's been on the table
4 before.

5 So if you use body weight divided by 70 to
6 the 0.75 power, the exponent there, which is a
7 standard scaling exponent, is okay in certain
8 situations probably in children over age 8, and may
9 become less accurate in children under age 8, and
10 certainly is less accurate as a way to get to a
11 standardized starting dose scaling from an adult
12 dose that you think works.

13 Then that's more complicated depending on
14 the genetics of clearance because there are plenty
15 of specific situations where clearance is different
16 depending on the age of maturation of different
17 clearance enzymes, efavirenz under age 5, I think
18 cyclosporine under age 8.

19 So these things, the appropriate dose, or
20 the appropriate scaling exponent, when you're
21 scaling allometrically, changes dramatically
22 probably under age 8, and certainly under age 2,

1 and then is different again in the very low birth
2 weight.

3 If this is really about trying to choose a
4 dose that gets you to the adult, the median adult
5 exposure, if that's what you're going to say, I
6 think those studies need to be done in a stepwise
7 fashion back from about age 8 down, to show that
8 you can choose the right dose just to get the right
9 PK.

10 Is that part of the question?

11 DR. HERTZ: Yes. The cleanest setting for
12 extrapolating efficacy from adult is if you expect
13 to have the same PK/PD relationship. So if we do a
14 study in children based on our best understanding
15 of how to create that starting dose, prior
16 experience, reference materials that are generally
17 accepted in pediatric clinical settings, what we
18 know about the PK of the drug in adults, the
19 exposure in adults, and the maturational age of the
20 appropriate metabolic systems in a population, the
21 pediatric population, we try to target a comparable
22 exposure to the adult dose.

1 Then we get safety information. Those
2 patients often have the opportunity, depending on
3 the type of study, to be titrated further to
4 effect. We use that add-on method that I've
5 described. In this case, it's often if we're
6 extrapolating efficacy open-label, so we don't even
7 have a comparator. We're just looking at some
8 general supportive information that we can collect.

9 But sometimes we miss that target PK
10 exposure, and then the question is, is the
11 underlying idea that that extrapolation should
12 simply be based on a similar exposure sufficient,
13 or do we need to do more? So do we need to simply
14 titrate the dose until we get matching exposure, or
15 should we then start to collect clinical data
16 instead if the known dose from these other sources
17 doesn't in fact provide the exposure we expected?

18 DR. HAVENS: [Inaudible - off mic].

19 DR. HERTZ: If we do what everyone here has
20 said in terms of trying to sort out that initial
21 dose, we look at available experience and
22 references, and that dose misses the PK target, do

1 we simply adjust the dose, or do we reconsider the
2 need to get actual clinical efficacy data?

3 DR. BROWN: I want to make one comment, and
4 then I want to get to Dr. Nelson. This begs the
5 question, your comments, of whether or not there's
6 some way of determining why, or in what
7 circumstance, that there's variability in the
8 development of these PKs in different drugs and
9 different patients.

10 Is it random or is there something specific
11 that you can base your analysis on? If it in fact
12 is random, I don't see how you can know from one
13 patient or one drug to the next whether or not
14 you're going to be able to extrapolate from that
15 drug if indeed it's random.

16 So if you can identify a characteristic or a
17 set of characteristics that allow you to have some
18 understanding of why this occurred, then I think
19 that it would be safe to assume that you could
20 identify a safe starting dose based on extrapolated
21 adult data. Without that knowledge, I'm not
22 certain that I can see that happening.

1 DR. HAVENS: But part of the issues you're
2 arguing about PK, which itself is really
3 complicated to try to get the right initial dose.
4 Choosing the extrapolation model is really
5 different, and over and over and over again, people
6 have chosen models that underestimate the dose
7 needed, especially young babies, just to get the
8 PK.

9 This question mixes the issue of achieving
10 the target PK with does a child need a lower plasma
11 concentration or drug exposure to get the same
12 benefit?

13 So for me, those are separate questions
14 because over and over and over again, just dividing
15 by the adult weight of 70 does not get you to the
16 appropriate milligram per kilogram dose. And even
17 using standard allometric scaling might also miss
18 the PK target, independent of the PD that is
19 implicit in the way this question is written.

20 DR. BROWN: Dr. Nelson?

21 DR. NELSON: Just perhaps to set the context
22 a little bit in terms of the language of

1 extrapolation, I didn't go over this much
2 yesterday, but you might remember the one slide
3 where I alluded to full extrapolation versus
4 partial extrapolation.

5 So as a reminder, full extrapolation would
6 be where you work out the dose, and it may be
7 complicated to do so, where if you get that same
8 blood level, plasma level, that you get the effect
9 you want. So full extrapolation would be PK only,
10 independent of what dose you have to do to get
11 there. And that could vary depending upon
12 absorption, distribution, and so on, and then
13 safety. That's full extrapolation.

14 Partial extrapolation can range all the way
15 from you need some PD, and that could be to a
16 biomarker endpoint, or let's say stress cortisol in
17 the case of pain. I'm not suggesting that's a
18 biomarker, just pulling that out of a hat. Or it
19 might have to be a clinical endpoint, like a FACES
20 scale or some standard scale, but yet not powered
21 to efficacy to where you can show an
22 exposure-response relationship that supports your

1 willingness to extrapolate efficacy.

2 That would be the partial extrapolation
3 paradigm, and that could range all the way from
4 some small PK/PD type study that reassures you that
5 you're doing the right thing, to a full clinical
6 trial if you're not that sure. So there's a large
7 territory, if you will, that's covered by that idea
8 of partial extrapolation. So I think it's just
9 important to keep that in mind.

10 As I see this question, it's basically
11 saying -- well, what you're saying, Peter, as I
12 hear it, it's one question to say is the PK target
13 different. But one would be, if in fact at that PK
14 level, which was efficacious in adults, it's not
15 efficacious in children, what then should be done?
16 Do we just need PK/PD to some pain thing, or do we
17 need to do full efficacy? So there's ways of
18 viewing that. But that's sort of the paradigm, if
19 you will, that this question is playing with.

20 DR. BROWN: But that's the crux of the
21 argument. And I guess my question would be, how
22 does one define the next steps here. And I'm

1 asking this question of everyone around the table,
2 because that knowledge there that you're speaking
3 of, again, is right now an unknown. You don't know
4 why there's variability there. And it could be
5 random or it could be some scientific reason, or it
6 could be that the drug's in another universe.

7 DR. HAVENS: When you say variability, are
8 you talking about PK variability or variability in
9 the PK/PD relationship?

10 DR. BROWN: I'm talking specifically about
11 the PK data, without necessarily including the
12 PK/PD relationship, because that is the way the
13 question is asked.

14 DR. HAVENS: PK variability with age is drug
15 specific, essentially. So you have to establish
16 the dose-to-exposure relationship for each drug at
17 different age and maturity. And for some drugs,
18 there can be dramatic differences by age. So for
19 certain antiretrovirals, which I know best, the
20 unboosted atazanavir, to get the same plasma
21 concentration as an adult would get and get cured,
22 it requires 2 to 4 times the adult dose in an

1 adolescent.

2 Some adolescents being very big and having
3 great livers, metabolize the drug so rapidly that
4 they need higher than what is called the maximum
5 adult dose to get the same amount of drug in their
6 body. So the PK, the dose-to-drug exposure
7 difference is drug specific and age specific.

8 DR. BROWN: Right. And I think that the
9 scientists at the FDA probably keep that in mind.
10 And I think that, Sharon, if you can bail me out
11 here, but you're talking about a situation where
12 there's a completely unexpected finding that
13 creates a circumstance where you cannot utilize the
14 routine methods of extrapolating from adult to
15 pediatric doses.

16 DR. HERTZ: Yes. We've had some good luck
17 with some of our pediatric programs. When we
18 initiate pediatric dosing based on available
19 information, and the literature, in practice,
20 guidelines, and we see how the clinical trials are
21 constructed, and then we get the initial PK data,
22 we see that there's often a fairly good expected

1 outcome.

2 The PK that we were hoping to achieve is
3 achieved. There's a good amount of information
4 that was accurate in terms of helping to define the
5 initial PK dose. And that goes a long way in
6 helping us extrapolate the efficacy from adults to
7 children.

8 We've had one experience so far where we
9 didn't get a good match in the PK, and it left us
10 wondering a number of things. And we're going to
11 be exploring that with the company involved a
12 number of different ways. But it raised the
13 broader question of, when standard dosing, either a
14 textbook, a Harriet Lane kind of thing, articles, a
15 clinical experience from the investigators, when
16 the doses that are traditionally used don't end up
17 providing similar exposure to adults, where we go
18 from there.

19 If the support for that dose is based on
20 clinical experience, do we negate that experience
21 even though it's not been systematically collected?
22 So that's one question, do we believe the dosing,

1 or do we then instead say we need to get clinical
2 information, which in the traditional way in this
3 setting is very challenging, given much of what's
4 been said about understanding response,
5 pharmacodynamic responses in some of these patient
6 groups.

7 DR. BROWN: Dr. Lasky?

8 DR. LASKY: Thank you. I wanted to build on
9 Dr. Ruha's comment about observational data,
10 collecting information about how clinicians are
11 dosing specific groups of patients to fill in the
12 matrix. And I'm thinking that it should be
13 possible to query certain kinds of electronic
14 healthcare records or databases to fill in a
15 picture of what current practice is. And I've been
16 thinking about it as the discussion has been
17 proceeding, and I'm sort of encountering the kind
18 of analogous problem in my mind.

19 We don't have a national database that we
20 can query and get a national estimate of what
21 clinicians are using for whatever condition in
22 whatever age group. And it's pretty well

1 documented that there's a lot of variation across
2 hospitals and across systems.

3 So there's an issue here in terms of
4 querying a system and then doing something similar
5 extrapolating to the United States and saying this
6 is the range of doses that are used in certain
7 conditions.

8 But I think this should certainly be
9 explored, and it does provide some kind of body of
10 information about what Dr. Kibbe was talking about,
11 what clinicians feel comfortable prescribing. And
12 then I suppose, and I'm just going out on a limb
13 here to the statisticians, this could be
14 incorporated in some kind of a Bayesian way as
15 prior knowledge, and then brought into calculations
16 in terms of next steps in thinking about dosing.
17 So I'm throwing them out there, and I'm not sure
18 where these ideas might all lead.

19 DR. BROWN: Dr. Flick? Dr. Neville?

20 DR. NEVILLE: The more we talk about this,
21 the more I have no good answers. I think in my
22 mind it's somehow a combination between the two.

1 So I think to negate all the -- and it hurts my
2 heart to say we can't extrapolate, but I don't
3 think we can. But to negate all of the clinical
4 experience that's out there to do a full efficacy
5 trial we know is incredibly challenging. But to
6 not do any efficacy, I think is also problematic.

7 So could there be a confirmatory smaller
8 pilot based on titrating to effect evidence? So
9 it's almost in my mind like a compromise because a
10 full trial will take years and we'll never get it
11 done. But I think if we just titrate to effect,
12 we're back in the pre-BPCA, PREA days. So I think
13 we have to find something in between. I don't know
14 exactly what that is, but I vote for choice C.

15 DR. BROWN: Dr. Wade? Dr. Havens?

16 DR. HAVENS: Thank you. I think I may
17 finally understand your perspective, which has been
18 really hard for me to get to. But what you're
19 suggesting is if the standard dose that we are all
20 using, we have chosen because it seems to give the
21 effect we want, but it gives a non-adult PK answer,
22 then almost by definition you've described, you've

1 defined, that the PK/PD relationship in children is
2 different than in adults.

3 One approach to that would be to titrate
4 either to effect, to clinical effect, or to titrate
5 to the adult PK showing that that was toxic or
6 otherwise perhaps gave better benefit. So if the
7 standard dose that you've chosen to start with
8 gives low PK, you've almost demanded that you
9 continue the study.

10 Then the two questions are, do you study to
11 a clinical endpoint and measure the PK that got you
12 to a different clinical endpoint, or do you titrate
13 to what you'd call adult PK target, and see if the
14 clinical endpoint that we might have accepted in
15 children is really the wrong clinical endpoint or
16 more toxic than it would be in adults. I'm
17 presuming that we're getting too low of a dose
18 initially, or exposure.

19 DR. BROWN: Dr. Czaja?

20 DR. CZAJA: So just a couple of things. I
21 think first is probably I'd like to understand a
22 little bit better the implications of your

1 question. So are you asking, one, should we gather
2 more data on this question, period; or two, we are
3 going to gather this data in order to make a label
4 change that's based on extrapolation, as has been
5 done with other drugs?

6 I ask this because I think one of the
7 challenges that we're dealing with, with this
8 particular class of medications, is that unlike
9 other conditions, the outcome is going to be highly
10 variable. So to titrate to effect is really an
11 important aspect. So like we're going to cure
12 cancer, or we're going to completely cure an
13 infection, the degree of being able to treat pain
14 is going to be highly variable.

15 I think when you're talking about a safe
16 starting dose, many children are probably going to
17 need some titration, if we're focusing purely on a
18 safe aspect. And I think a lot of the discussion
19 from yesterday and from today point you toward
20 needing more data, however you choose to obtain it,
21 to be able to dictate a safe starting dose,
22 especially if a good proportion of those

1 medications -- or you may take it as an outpatient,
2 where the kids are not being monitored for some
3 other really serious adverse effects that we're
4 worried about.

5 DR. BROWN: Dr. White?

6 DR. WHITE: Thank you. I need just a quick
7 clarification. Are we discussing using an
8 extrapolation only down to 2 years of age, or are
9 we discussing extrapolation across the range of
10 pediatric patients?

11 DR. HERTZ: Right now, we only go to age 2
12 with extrapolation.

13 DR. WHITE: Okay.

14 DR. HERTZ: So I'm just going to sort of
15 create the scenario of an old opioid, drug A, being
16 used for years. We don't have systematic
17 collection of efficacy data because it's very old,
18 and for a number of the reasons that we've heard.
19 It's very difficult to study. There's a lot of
20 patient variability in terms of exposure based on a
21 variety of things that may be impacting the
22 maturation of underlying metabolic pathways;

1 concurrent medications; and individual variability
2 in general.

3 So, if we do a clinical study, relying on
4 existing practice-based, experience-based dosing,
5 and the resulting exposure is low, there are two
6 options. If we want to continue to try and
7 extrapolate, we can adjust the dose to be
8 comparable to the adult exposure, and then do
9 additional PK and safety on that dose; or we can
10 try and collect clinical data at the lower exposure
11 to see if that's an adequate place.

12 Now, neither one seems particularly onerous
13 until you start to think about doing this in 2 year
14 olds. And if this was an adult question, it would
15 be fairly straightforward in terms of next steps
16 because the ease of conducting studies in normal
17 volunteers would clear the path to do a variety of
18 ways to get the information we need to fill in this
19 gap. But because of the nature of doing these
20 studies in children, with all the challenges that
21 we've heard about, and the challenges in getting
22 pharmacodynamic endpoints, easier in a 2-year-old

1 than a 25-weeker, but still challenging.

2 So the question is, should we push ahead and
3 try and adjust the dose to meet the adult exposure?
4 Should we regroup and reconsider whether
5 extrapolation is appropriate, and then go after the
6 clinical efficacy study, which then becomes the
7 more complex, but you know, potentially doable, a
8 blinded study with our traditional add-on design?

9 We're just trying to get a feel for the
10 comfort of relying on the more general clinical
11 data out there versus not being comfortable with
12 that. I'm kind of getting a sense of a desire for
13 more information, but as Dr. Neville said,
14 recognizing that it's going to be a difficult
15 challenge if we have to go into the full efficacy
16 realm.

17 Again, when we developed our current
18 approach for analgesic development in children,
19 trying to determine the extent to which we could
20 rely on extrapolation of efficacy, it was in part
21 because we know how difficult it is to get these
22 studies done. They are difficult to enroll, and

1 there's a lot of noise, much more so than in adult
2 populations, just based on the sensitivity of the
3 instruments to measure pain.

4 The fact that pain is traditionally
5 self-reported, until you get to an age range that
6 is unable to do that, and then you have a clinician
7 reported assessment, the nurse, the caregiver, the
8 family member; somebody else is going to assess the
9 pain.

10 So the ability to rely on extrapolation
11 takes a lot of the burden off getting studies done
12 because open-label studies with just an add-on,
13 where you use sparse sampling, PopPK, is not as
14 difficult. They're not easy. I'm not trying to
15 say that they're simple, but they're not as
16 complicated and difficult to get enrollment, and
17 then analyze as, obviously, a dedicated efficacy
18 study.

19 DR. WHITE: Thank you. That helps a lot in
20 trying to figure out the question you're actually
21 posing, because if you look at this in terms of
22 drug development, and it's a new drug that we don't

1 have a whole lot of experience with, I don't think
2 extrapolation would be the appropriate choice in
3 light of there may be phenotypic variations. There
4 are many, many things that haven't been
5 established.

6 If there's a long clinical history and
7 there's lots of data regarding what's a safe dose,
8 then I think it's a good choice to start with that
9 safe dose, but I still think we need to demonstrate
10 efficacy. And if it's published here, there, and
11 everywhere that this is a drug that we use for
12 pain, and we have what we think is a safe dose,
13 we're still not convinced of efficacy in children,
14 I don't think.

15 I think you go in with a pre-conceived
16 notion that this is a good drug for pain, and you
17 give it to the child, I think many of us would go,
18 okay, I gave a good enough dose, it must be okay,
19 even though we've never demonstrated efficacy.

20 The problem that we get into is the one that
21 was demonstrated today -- and I'm sorry, I can't
22 remember the speaker -- is that the placebo effect

1 for control of pain is tremendous. It's sometimes
2 difficult to demonstrate the difference between
3 placebo and a narcotic.

4 So if we were just using that, that data of
5 a safe dose, and prescribing the drug with no
6 efficacy data, I think we run the risk of putting
7 children at risk for the side effects of narcotics,
8 and all these bad things we're talking about that
9 narcotics can contribute to, with no efficacy, or
10 no proven efficacy. And simply accepting, oh yeah,
11 this is a good drug for this purpose because we've
12 approved it, it's in the label that it's there, and
13 this is the dose that you should use. So this is
14 the drug we're going to utilize for these kids that
15 are in pain, whether it really is an efficacious
16 drug or not.

17 Does that make any reasonable sense?

18 DR. HERTZ: Sure.

19 DR. BROWN: Part of this then turns on
20 whether or not this is a big problem or a small
21 problem. And it sounds like we're talking about
22 one evaluation here of one drug. And it would be

1 interesting to know, in the population of opioids
2 across the board, whether this is common or not
3 common.

4 The reason I say that is that there will be
5 new drugs that will be developed and new cultures
6 of current moieties that we don't even know about
7 yet. And if we don't have a clue how to manage the
8 older drugs that we've used forever, then I don't
9 know how we will be sophisticated enough to manage
10 the newer drugs as they come along. We've got a
11 lot of historical data for drugs that are kind of a
12 backstop to what we're doing. For newer drugs as
13 they begin to be developed, we won't have that.

14 Dr. Kibbe?

15 DR. KIBBE: Glad you came back. First, for
16 every complex problem, there's a simple answer, and
17 it's wrong. My goal was to get an element that
18 could be tracked, that was a relatively reliable
19 element. The element that I got was a direct
20 correlation between effectiveness and blood levels,
21 which means it was a PK/PD correlation.

22 Minimum effective concentration, as

1 determined by the patient telling you that I start
2 to feel pain now, means that the duration of effect
3 of the dose that you gave him is now ending. And
4 you now know the levels that you need to continue
5 to exceed in order to get continued therapy. And
6 if we do that in small groups and get some kind of
7 consistent number within each of those groups, then
8 we have a handle on how that progresses across
9 different disease states and different age groups.

10 Now, can we then generate a correction
11 factor for pediatric patients when we deal with
12 opioids? Well, we do that now with renal patients.
13 Percent of creatinine clearance can be used to
14 correct dosing regimen designs for drugs that are
15 excreted at least partially by the kidney.

16 We can change half-lives. And if you don't
17 believe me, just go pull your local antibiotic
18 labeling, and it will tell you if the creatinine
19 clearance is 120, you give it this way, and if it's
20 90, you give it this way, and so on. We can do
21 that now based on data across drugs within that
22 particular group of individuals, those with

1 impaired renal function.

2 Here we're dealing with a much more complex
3 situation because each opioid has a different
4 metabolic pathway, and there's no easy way of
5 measuring the liver function with a single test.
6 SGLT doesn't do that. So what we're going to get a
7 handle on is, for me, an experimental study to find
8 out what's going on during maturation of pediatric
9 patients by using opioids. And at the same time,
10 give people who are writing prescriptions for
11 opioids a sense of confidence that they can get to
12 a therapeutically effective amount for a given
13 period of time with a certain dosage regimen, and
14 that was what would come out of the data.

15 DR. BROWN: Dr. Harralson?

16 DR. HARRALSON: Yes, for some drugs, there's
17 a pretty clear correlation between amount and
18 effect. But in my opinion, opiates are an example
19 where that's very poor, that the relationship
20 between the concentration and the effect is not at
21 all clear, and it changes with time. So although
22 my background is pharmacokinetics and I like

1 looking at those relationships, this would be one
2 group of drugs where I think the result would not
3 be good.

4 The second thing is, if you consider a study
5 in which you raise the dose in a child to produce
6 an exposure equivalent to adult, that has no
7 benefit for the child. And having been an IRB
8 chair, that would not be an approvable study if the
9 only purpose was just to see if it were the same as
10 an adult. So I think that, if you were just simply
11 raising it to see exposure, would not be a study
12 you could actually do.

13 For me the idea would be to really just try
14 to understand the PK, which is very important. But
15 then when you're looking at adverse effects and
16 that sort of thing, it would be titrating to
17 effect. And at the point of effect, what is the
18 adverse effect profile for a particular age group?
19 And I think you have to decouple PK/PD to a certain
20 extent here.

21 DR. BROWN: Dr. Hoehn?

22 DR. HOEHN: Sarah Hoehn. Well, as a

1 disclaimer, I'm the opposite of a pharmacologist.
2 I find all this PK/PD stuff confusing. But in
3 terms of the answers to the question, I think
4 similar to what Dr. Neville said, I think there has
5 to be some middle ground. And I think you're going
6 to have acknowledge that there's not going to be
7 big large studies that are done over this. And I
8 think they're not going to be able to be done in
9 the outpatient setting.

10 The way I see it playing out over time is
11 people are just going to have to do different
12 studies, both looking at efficacy and
13 extrapolation, but looking at different
14 populations. So people have mentioned doing a
15 posterior spinal fusion population, and doing
16 something where people are already in the hospital.
17 And you can do some of the PCA studies and just see
18 if they're getting a good response from it, and
19 you're also looking at toxicity.

20 I think there's other different populations,
21 but I think these studies are going to have to be
22 done in an inpatient setting. Some people have

1 mentioned healthy children, and I really think it's
2 not going to be appropriate to ever try an opioid
3 in a healthy patient, in a child. It's just never
4 going to be appropriate. But I think there's other
5 populations, whether it's neuroblastoma kids or
6 osteosarcoma kids, or different kinds of
7 oncological processes where they have really,
8 really severe bony pain, and those might be times
9 that they could certainly be studies done on very
10 specific populations.

11 I think whenever you do a population like
12 that, a study like that, there's a thousand
13 confounders because of what chemotherapy and
14 different treatments have done to their metabolism.
15 But I think the only way to find, to look at this,
16 is to have different pilot studies that go on.

17 Really, the only way I think you'll be able
18 to look at this in children without a lot of
19 confounders and comorbidities is going to be the
20 post op patients, whether it's spinal fusion or
21 other high risk T&As that are otherwise in the
22 hospital. I just don't think it's anything that

1 will be able to be done, ethically, morally, or
2 feasibly, on an outpatient basis.

3 DR. BROWN: Dr. McCann? Dr. Flick?

4 DR. FLICK: I want to get back to something
5 that you asked, Rae, is about the magnitude of this
6 and how many drugs are we talking about that we
7 would have to study. All of these drugs are
8 formulated differently in children than they are in
9 adults, so you have different absorption. So that
10 makes it more difficult to extrapolate in those
11 settings.

12 If a pediatric formulation is going to be
13 labeled for use in children, then you're going to
14 have to study each one of these different products
15 and formulations. Is that right?

16 DR. HERTZ: To a large extent, but not
17 uniformly. The exposure to the opioid is pretty
18 reliably proportional to the dose for most of our
19 products, regardless of the formulation. There are
20 some exceptions of that, at least in adults. So if
21 you're converting across different products, or
22 from IR to ER, we have a fair amount of information

1 about that for many products.

2 DR. FLICK: I'm actually wondering about the
3 change from a tablet to a liquid.

4 DR. HERTZ: Right. So again, even for that,
5 we have a pretty good idea in the adult population.

6 DR. FLICK: Okay.

7 DR. HERTZ: And one of the things that's
8 done in the beginning to understand some of the
9 relationships in adults and pediatrics is -- and
10 again, we don't do these in normal children; these
11 are in children who otherwise need to be managed
12 with the opioid -- we look at relative PK studies
13 for a dose of the pediatric formulation in the
14 pediatric setting, and we'll test that new
15 formulation in the adult to create a bridge to
16 understand some of those gaps.

17 We don't try to force an adult formulation
18 where it doesn't fit, but we will do the opposite
19 in the adult. So the link across formulations is
20 one we can manage on the adult side, and then we
21 just need one bridge to the children.

22 DR. NELSON: Skip Nelson. I would just

1 reinforce that. Bioequivalence studies that we're
2 often referring to are done in adults, since we
3 don't think you need to use kids to do that. Those
4 data would be available before you then moved into
5 the population to sort out your PK/PD in a
6 therapeutic setting.

7 DR. NEVILLE: I just wanted to sort of echo
8 and agree with Dr. Hoehn that I think sometimes the
9 inpatient population is underutilized, and that may
10 help solve some of these issues. And we've talked
11 about some of the patient populations that might be
12 helpful.

13 I also wanted to distinguish, in the
14 question we have not distinguished between
15 immediate release and long acting. Given I
16 think -- at least what I've seen in some of the
17 trials for the long acting, I think if you're
18 talking long-acting drug, that's going to be even
19 more challenging. So again, I would say somehow,
20 it's going to have to be something in the middle,
21 especially for the longer acting agents.

22 DR. BROWN: Any other comments?

1 (No response.)

2 DR. BROWN: Well, this is clear as mud.

3 (Laughter.)

4 DR. BROWN: What I'm hearing is that we have
5 a large amount of historical data about the use of
6 many of these drugs in many children. Some of
7 these patients, the ability to use adult PK data
8 does not follow except in models, for reasons that
9 are not clear. And it's also not clear whether
10 this is common to many drugs or just a few.

11 But if it occurs, it may follow that a safe
12 starting dose by using experienced dosing trial
13 based on the history of use -- in other words,
14 rather than having an efficacy trial, going to
15 establishing a safe starting dose from historical
16 data, and then requiring efficacy data if that data
17 was found to be incomplete.

18 The examination of data relating to these
19 drugs is difficult, will need to be examined in a
20 unique way, and may combine the use of known data
21 for starting doses and extrapolation to other
22 populations. Obviously we've spoken a lot about

1 the fact that the pediatric population is very
2 granular. So the matrix, as Dr. Kibbe calls it,
3 will have a lot of cells.

4 Opioids, however, may be a special case,
5 that extrapolation doesn't fit for all patients for
6 all drugs, and that's obvious from the question.
7 For those indications, may need more complete data
8 and larger studies. And as we've just heard,
9 there's some sense that those larger efficacy
10 studies, if they're done, may need to be done in an
11 inpatient setting in post-surgical patients.

12 Does that capture a little bit of what
13 anybody thought that we said?

14 (No response.)

15 DR. BROWN: Let's move on to question
16 number 5. And question number 5 for discussion,
17 you have heard about significant challenges
18 associated with the study of opioid analgesics in
19 pediatric patients. Discuss possible approaches to
20 overcome these challenges.

21 Is that clear? Is that question clear to
22 everyone? Is that a question that we can answer?

1 Any comments or questions? Dr. Patrick?

2 DR. PATRICK: Just a couple quick things to
3 reiterate. Partnering with other organizations to
4 gather some of these secondary data, including the
5 Children's Hospitals of America, where a large
6 proportion of our complex children are taking care
7 of, there are claims data that are linked to
8 medications. And that may be a useful source as
9 well as the other things we've discussed, the
10 Neonatal Network, as well as Vermont Oxford
11 Network.

12 DR. BROWN: Dr. Higgins?

13 DR. HIGGINS: One particular challenge that
14 I've heard a lot about in the last couple days is
15 the enrollment or recruitment for pediatric trials,
16 and this is something that I find particularly
17 frustrating. I used to be a patient recruiter for
18 Alzheimer's trials, as well as other neurological
19 diseases, and worked tirelessly to get guardians or
20 caregivers to sign on to these trials.

21 It was a real challenge, but I think with
22 the right educational campaign, if there was such a

1 thing, to have an educational campaign educating
2 parents about the benefits of trial participation,
3 I think we'd go a long way in boosting those
4 enrollment rates.

5 DR. BROWN: Dr. Turer?

6 DR. TURER: Thank you. Christy Turer. So
7 one thing that I thought about is, there are
8 certain conditions that absolutely warrant opioids.
9 And then the question really is, what is the
10 starting dose that is needed, and what is the
11 correct duration of use? So, that's one pot of
12 conditions.

13 Another one that is less clear are
14 conditions in which it's controversial whether
15 opioids are really needed. So for example,
16 fracture, particularly in adolescents who are going
17 to be prone to them either because of football or
18 because of other athletic issues, who would be at
19 greater risk for abuse potential in that
20 developmental period.

21 Could there be a role for randomized trials
22 where we randomize people who have, let's say, risk

1 fractures or arm fractures? Not so much femur. I
2 mean, some of these are clearly, that would warrant
3 stronger pain medication. But then randomize
4 people to either getting NSAID versus opioid
5 Tylenol, or just Tylenol alone, and see, do we
6 actually need opioid. Because maybe the starting
7 dose in certain populations of opioid is zero, and
8 I think that would be really meaningful in a
9 population that's at great risk.

10 DR. BROWN: One way to do that, rather than
11 giving no opioid, would be to use -- and folks have
12 done this in the past, look at opioid sparing by
13 giving -- and we've spoken quite a bit about
14 multimodal therapy, and I think that's what people
15 have been trying to get at.

16 Dr. Emala?

17 DR. EMALA: I see one of the major
18 challenges of accomplishing a lot of what's been
19 discussed over the last two days is funding these
20 types of studies. So we've I think had unanimous
21 agreement of the need for more data, and a lot of
22 granular discussion about what types of studies

1 might be warranted. But some frustration discussed
2 yesterday where investigator-initiated studies that
3 are submitted to the NIH are not very well
4 received.

5 I think there's also some frustration
6 sometimes when priorities of one federal agency
7 don't get transmitted to another, imperatives such
8 as this for the FDA being conveyed to the
9 respective institutes of the NIH.

10 So I think it would be a very important
11 component of getting over these challenges for the
12 FDA to be working in concert with the NIH,
13 minimally at an RFA type of approach, if not a U19
14 type of approach, because I think, although the
15 vast majority of NIH research is funded by
16 investigator initiated studies, that often falls on
17 the deaf ears of uninformed study sections; whereas
18 if there's actually a call for applications, an RFA
19 or a U19 mechanism, I think the chance of having
20 funding for these great plans, which will remain
21 great plans without appropriate funding, will be
22 incomplete.

1 Secondly, I think in our background
2 information, we read a little bit about the
3 responsibility of industry and industry funding for
4 these types of studies in pediatric pain
5 populations. And there apparently is already an
6 initiative where industry is incentivized to invest
7 in these types of studies by having the exclusivity
8 of their products extended for a period of six
9 months.

10 So I wonder if that's enough of an incentive
11 to have industry fully vested in funding these
12 types of studies, or whether even a REMS type of
13 program that's the responsibility of industry to
14 fund could be incorporated. But I think at the end
15 of the day, great plans will remain great plans
16 unless there are active efforts at the federal
17 level to have these types of studies funded.

18 DR. HERTZ: I just want to correct one
19 little thing, because sometimes things can snowball
20 a little bit. REMS authority doesn't really give
21 us the opportunity to require the kinds of efficacy
22 studies, development studies that we've been

1 talking about.

2 The authority we have to require that of
3 industry would come under the pediatric legislation
4 that you've heard about, PRE, where we can require
5 it for the product in the indication, or BPCA, if
6 they want to seek pediatric exclusivity, and then
7 we study the moiety across all relevant uses.

8 So the REMS is about safety features
9 necessary for maintaining the risk balance as
10 opposed to gaining this type of new study. So I
11 just wanted to clarify that.

12 DR. EMALA: I wasn't suggesting that this
13 would be appropriate in a REMS program, I was just
14 curious if analogous types of obligations could be
15 extended to industry like the REMS program was.

16 DR. BROWN: Dr. Draker?

17 DR. DRAKER: Bob Draker. Does the FDA have
18 any access to the I-STOP data available in certain
19 states? Only because in New York State, we see a
20 lot of that information that would be very valuable
21 at the state level with regards to getting
22 demographics on who the prescribers are, the age

1 groups and the locations of the recipients. Some
2 states have that, but that really gives you quite a
3 bit of information with regards to prescriber
4 practice, and the approaches taken for certain
5 diagnoses as well.

6 DR. HERTZ: Can you restate the name of that
7 database?

8 DR. DRAKER: It's called I-STOP, which --

9 DR. HERTZ: I-STOP.

10 DR. DRAKER: -- is through the DEA. Some
11 states have adopted I-STOP. It's where you call
12 in. Any time you're going to use a controlled
13 substance, you register the particular patient.
14 And the database, the statewide database, allows
15 you to look at -- or the state does, to look at
16 information with regards to the number of
17 prescriptions, when they were filled, who they were
18 prescribed by.

19 DR. NELSON: Skip Nelson. My understanding
20 is that many of those programs are voluntary; at
21 least where I have my license, I got an email
22 saying do you want to participate. But obviously

1 I'm not prescribing these being at FDA, but my
2 impression was, it was a voluntary program, which
3 would undermine the quality of the data.

4 DR. DRAKER: That program is not voluntary;
5 it's mandated in New York State.

6 DR. NELSON: Well maybe in New York, but not
7 in my state.

8 DR. BROWN: Yes. This varies state by
9 state. There are still a few states that are not
10 requiring that. But you're correct that there are
11 lots of states that do require that. For example,
12 in a state like Kentucky, where we have a big drug
13 problem, it's been very useful in helping us change
14 the behavior of both physicians and patients.

15 DR. DRAKER: In New York State alone,
16 there's been a tremendous decrease, in the two
17 years that this has been very active, in the use of
18 opioid and other controlled substances.

19 DR. BROWN: Dr. Walco? Dr. Crawford?

20 DR. CRAWFORD: Thank you. Stephanie
21 Crawford. To pick up a little on what Dr. Emala
22 was stating in terms of a lot of the issues

1 yesterday, especially that were raised with the
2 funding, and it has been stated a lot today that
3 the condition of pain does not affect only
4 monolithic cohorts; it's so widespread. So maybe
5 in terms of those who are looking at conducting
6 studies, expanding the potential funding sources,
7 either from FDA or in add on with others, or just
8 other funding mechanisms.

9 For example, it could be -- some research
10 questions very focused could possibly be add-on
11 questions with respect to rare disease research
12 funding mechanisms for a certain, for example,
13 pediatric cancers or sickle cell or Ehlers-Danlos.
14 It's just many diseases, but it might be a
15 different way. And maybe one of FDA's roles could
16 be consideration of one or two, three focused
17 research questions that could be part of any such
18 study in any co-funded area.

19 One of the issues for me that's always of
20 interest with any research studies is, if we go
21 back to the ethics talks, distributive justice,
22 fair distribution of the benefits of the study as

1 well as the burdens.

2 Oftentimes, we'll see excellent studies that
3 are conducted, but they may be only for patients in
4 a low-income, urban setting, or extraordinarily
5 affluent suburban settings, or observational
6 studies that are Medicaid only or commercially
7 insured only for covered individuals.

8 So I would just ask that there be
9 encouragement of any pediatric studies in this area
10 that will look at a wide mix of patients.

11 DR. BROWN: Dr. Neville?

12 DR. NEVILLE: Similar to that, I'm sitting
13 here thinking, wondering if there is a way to
14 leverage BPCA, because none of the older opiates,
15 at least to my knowledge, are on the desired drug
16 list. And I understand funding, even for BPCA, is
17 an issue, but I can say we were somewhat successful
18 with hydroxyurea, an old drug that no sponsor
19 really was interested in because it was off patent.
20 And there may be some way to pull it all together
21 with NIH through that mechanism, at least for some
22 of the older drugs.

1 DR. BROWN: Dr. Patrick, did you have -- are
2 there any other comments surrounding this question
3 about the possible approaches to the challenges
4 that have been identified?

5 (No response.)

6 DR. BROWN: If not, some of the challenges
7 that we've heard over the last two days relate to
8 many things, but largely about two things, funding
9 and fear. I think it's been identified that the
10 NIH is a possible source of funding. I haven't
11 heard anybody suggest a larger group that might be
12 more useful. I think there are other data sources,
13 but for a source of dollars to provide to
14 individual or groups to get these studies done, the
15 NIH seems to be the natural source.

16 In terms of fear, fear for your career if
17 you do these studies, fear of hurting somebody, I
18 think the AAP again, I said this yesterday, could
19 be very helpful because this is a marketing issue.
20 And I don't think that the FDA can probably be, at
21 least in part, involved with this. And currently
22 the FDA and the AAP have a good working

1 relationship, so that they could market the need
2 for these studies to be done.

3 In terms of getting to some of the specifics
4 of the challenges, identifying data sources, and
5 we've heard about a variety of different data
6 sources and consortia that might be used. One of
7 particular interest would be the Oxford data
8 source. I suggested yesterday that Medicaid data
9 might be able to be used to an advantage, as well
10 as DEA data.

11 It was suggested that there needs to be some
12 kind of education process around the need for these
13 studies for all patients. And again, this is
14 probably within the realm of the American Academy
15 of Pediatrics.

16 When we talk about industry and how industry
17 can be effective, over the course of the last two
18 days I've been trying to think about what there is
19 available to pull industry into this. And in
20 reality, it all comes down to whether the extension
21 of their license for drugs is incentive enough for
22 industry to be involved, and it currently is not

1 apparent that it is. So at the very least, some
2 thought needs to be given to rethink the incentives
3 that industry currently has under PREA to get the
4 studies done that are required.

5 Does that sum the group?

6 (No response.)

7 DR. BROWN: So let's go on to our last
8 question. And the last question is, provide
9 additional comments that you believe are important
10 to address issues related to the use and study of
11 opioid analgesics in pediatric patients.

12 Is that a question that we can answer?

13 (Laughter.)

14 DR. BROWN: Dr. Turer?

15 DR. TURER: I don't know if this is out of
16 left field, but increasingly it seems that there
17 are a lot of athletes talking about their issues
18 with pain killer abuse. So in thinking about
19 avenues of funding, it might be worthwhile to tap
20 into the NBA, the NFL, and look for partners that
21 are higher profile, especially adolescents. They
22 may resonate with them some more. So outside of

1 the medical venue, but nevertheless, I think a
2 potent source of influence.

3 DR. BROWN: Dr. Hertz, do you think that the
4 FDA could partner with the NBA?

5 (Laughter.)

6 DR. BROWN: Or do you reject that out of
7 hand?

8 DR. HERTZ: I'm going to head that
9 committee.

10 (Laughter.)

11 DR. BROWN: I know there must be other
12 comments. Dr. Crawford?

13 DR. CRAWFORD: It's a comment to send back
14 to the group. I've heard several talk about the
15 need for other education and the use, but I don't
16 know the answer, but may I ask if the chair or any
17 member of the committee could make more specific
18 recommendations about how to increase education on
19 appropriate prescribing and monitoring?

20 DR. BROWN: Well, the FDA through the REMS
21 program certainly has a readily established
22 organizational structure that requires almost all

1 of pharmaceutical industry now, who create
2 individual opioid drugs, to create educational
3 programs.

4 Now these programs, for the most part, are
5 related to the prescriber, but I can see that could
6 easily be extended to the patient. And I think
7 some responsible pharmaceutical companies have
8 already done that. We've talked about Accutane a
9 lot. The program that was created for Accutane was
10 created not by the FDA, but it was created by the
11 industry that was responsible for putting Accutane
12 on the market.

13 So industry is aware of the requirements,
14 and they can do this. The question is, what kind
15 of incentives are there that would be provided to
16 do that. With the REMS program, the incentives are
17 pretty stark. And in discussions that we had in
18 May, unfortunately prescribers haven't really taken
19 advantage of that. And I think that the FDA is
20 working internally on changing things up so that
21 that program will be more successful.

22 Other comments?

1 (No response.)

2 DR. BROWN: Dr. Flick?

3 DR. FLICK: Today the burning platform is
4 opioid abuse, misuse, overdose, death. In the
5 past, it was Accutane, or it's anesthetic-related
6 neurotoxicity, which is still an issue. Tomorrow,
7 in the future, it's going to be some other issue
8 related to drugs or drug approval. And each time
9 we sit around this table, the common theme is
10 always, we don't really have the data.

11 It would seem to me that it would be far
12 cheaper for both industry and government to come
13 together in the era of big data. We have
14 electronic health records that are linkable now.
15 We have very large electronic health record
16 databases at Kaiser. We have one. Optum has one.
17 There are many others.

18 We could produce data, or a dataset, that is
19 minable, so whenever these issues come up, we can
20 go to that database to answer the question, rather
21 than to approach each one of these issues as if
22 they're separate issues and deal with them in a

1 piecemeal way, which is extremely inefficient,
2 unsatisfying, and ultimately really expensive.

3 DR. BROWN: Thank you, Randy.

4 Dr. Hudak?

5 DR. HUDAK: Yes, one thought I had
6 was -- and I'm not aware to what extent this may be
7 occurring already, but the reference was made this
8 morning by one speaker to the CDC's document they
9 released in March as a public policy statement on
10 opioids. And there were 12 specific
11 recommendations in that document. It was a very
12 thoughtful document, very well researched. And to
13 the extent that some of these recommendations might
14 be able to be applied by FDA at the class level to
15 these opioids, that might be something the FDA
16 would want to certainly carefully consider.

17 DR. BROWN: Now, are you speaking of
18 expanding the CDC guidelines, which are not
19 operative below age 18, I believe, to the pediatric
20 age group?

21 DR. HUDAK: So, yes. I think some of these
22 things can be expanded by extrapolation certainly

1 to some pediatric age groups. So I think that's
2 something the FDA could take a look at and
3 consider. Certainly not all of these
4 recommendations belong in labeling, but I think
5 there are at least a couple that provide additional
6 information that would be helpful on the labeling.

7 DR. BROWN: Dr. Shoben?

8 DR. SHOBNEN: Yes, so I just wanted to state
9 for the record, one of the challenges I see is the
10 lack of good outcome data, particularly in younger
11 pediatric patients. So it's very easy in opioid
12 efficacy studies in adults that you have this very
13 nice patient report outcome about their pain. And
14 that probably works fine for adolescents because
15 they can also report on their pain very
16 straightforwardly.

17 It would be really nice if there was a
18 really good way to measure it. We've talked about
19 this a little bit in various comments, but I just
20 wanted to state that for the record and say that
21 it's really challenging to come up with novel trial
22 designs and better statistics and things without a

1 good outcome measurement.

2 DR. BROWN: Dr. Bateman?

3 DR. BATEMAN: I think we'd all agree that
4 left over medications that are not properly
5 disposed of that are put in the medicine cabinet
6 are an important source of opioids that end up
7 being misused or diverted. And I think part of the
8 solution to that is having prescribers prescribe in
9 a more judicious fashion, giving out a fewer days'
10 supply, or a supply that's titrated to what the
11 patients are actually going to use.

12 But another important component is just
13 having the patients throw away the leftover
14 medication. And what I found talking to patients
15 and other providers, is there's a lot of confusion
16 about how to do that. And I guess the label that
17 FDA has put on opioids suggest that they can be
18 flushed, but I don't think that message has really
19 gotten out there.

20 So I think that to the extent that FDA can
21 increase the awareness that these medications can
22 be flushed, and can encourage providers to educate

1 their patients about the need to do that, I think
2 that would potentially be an important step in
3 reducing the reservoir of these medications
4 available for misuse.

5 DR. BROWN: Dr. Lasky?

6 DR. LASKY: I realize as we're wrapping
7 things up, we do have a member of the committee who
8 is representing the patient voice, but we haven't
9 thought very much -- talked about the role of the
10 patient, the parents, and children as partners.
11 And there's a lot of different aspects of it,
12 particularly if we're talking about trying to get
13 funding through Congress or wherever else.

14 But there's a specific role, and I'm not up
15 to date on, and for Dr. Hertz, I know FDA is doing
16 a lot in terms of patient preferences and how this
17 could play into this area in terms of studies of
18 opioids in kids. However it is, that's an area
19 that would be good to explore and encourage.

20 DR. BROWN: Dr. Jones?

21 DR. JONES: My comments are really along the
22 same lines. I think this is really a public health

1 problem that a lot of people aren't aware of,
2 especially parents. So most parents probably don't
3 know that we don't really know the effective and
4 safe dose of an opioid to give their child, they
5 just assume that we are giving them the right dose
6 and that it's been studied. So I think engaging
7 the public in this problem would be important.

8 I'm an allergist, and we've all heard about
9 the EpiPen pricing. And I think one of the reasons
10 why we've heard of that is because everybody knows
11 you don't mess with food allergy patients, because
12 those parents will come out, and they will get you.

13 (Laughter.)

14 DR. JONES: So I think using some of those
15 same approaches in engaging the families and the
16 patients that this actually affects is important.
17 So if the FDA could partner with the AAP, partner
18 with parent organizations for sickle cell,
19 pediatric cancers, and really get the word out
20 about these are the problems that we're having with
21 studying these medications and can you help us with
22 solving some of these problems, I think that would

1 make somewhat of an impact.

2 DR. BROWN: Dr. Nelson?

3 DR. NELSON: I just wanted to ask a point of
4 clarification from I believe Dr. Bateman. You said
5 that medications can be flushed. I guess I've
6 always thought that it would contaminate the water,
7 and kill the fish, and all that kind of stuff.

8 Could you expand on that, please?

9 DR. BATEMAN: Dr. Hertz, can you help me
10 out?

11 (Laughter.)

12 DR. HERTZ: So, you may be interested to
13 know that we actually maintain a flush list here at
14 FDA, in conjunction with some other agencies,
15 because we don't want to put certain products into
16 the water supply, if it can be avoided. Part of
17 how we decide what should be on a flush list is in
18 part based on risk. And having opioids discarded
19 in the trash or someplace where there could be
20 accidental exposure or theft is a concern.

21 When water quality is assessed, opioids are
22 generally not on the list of things that are being

1 detected. So it doesn't seem that we're creating
2 too much of a problem, although I'm not sure how
3 many people are listening to that. But the
4 products that we're talking about here, the
5 schedule 2 and 3s, are all labeled for disposal by
6 flushing, because that is a very secure way to get
7 them out of the house, out of the reach of
8 unintentional or intentional exposures.

9 There are also -- I believe it came out of
10 ONDCP, the Office of National Drug Control
11 Policy -- other recommendations for disposing of
12 controlled substances, which include mixing them
13 with kitty litter or coffee grounds, and securing
14 them in a container in the trash, so making them
15 unappealing and disposing of them in a container.
16 So those are two ways that are possible.

17 Taking advantage takeback programs is
18 another good one, and I know there are more of
19 those than there had been in the past. We
20 certainly support that as well. Some localities
21 will accept controlled substances at local law
22 enforcement offices. So I would check ahead before

1 showing up at your local police department with a
2 bag full of something, but that is something that
3 we've heard about as well.

4 So I think that you can
5 consider -- depending on the amount and the
6 frequency, certainly we think flushing is the best
7 way to get them out of the chain of problems until
8 we have better options for other types of takeback
9 or send back programs.

10 DR. NELSON: I just might add to that, I
11 guess I consider myself to be pretty responsible
12 when it comes to that, and I've asked the
13 pharmacist and all that. I've never heard that
14 before. So perhaps to go along with patient
15 education, that might -- and education of the
16 pharmacists. I ask all the time. I have every
17 medication since, you know for the last 18 years,
18 at my house. So that might be something that you
19 could add, patient education, when it comes to
20 that.

21 DR. HERTZ: So I'll just bemoan the fact
22 that it's in our labeling, and I would like to add

1 for general consumption that people should please
2 read the labels. We spend a remarkable amount of
3 time trying to make sure that the information in
4 the labels is relevant and as up-to-date as
5 possible. We've been engaging in a number of class
6 labeling efforts to try and improve the information
7 in general and improve the consistency of delivery.

8 We've done a lot of work on the extended and
9 long-acting opioids. We are currently working on
10 the immediate-release opioids, which is a much
11 broader and older group of products. And I can
12 tell you, it's taking quite a bit of resources to
13 do this. But part of that will be to make sure
14 that they all have disposal instructions, which
15 will include, for this group, flushing.

16 I believe it's on our current medication
17 guide. I know that they're not always delivered
18 the way they're supposed to be at the time of
19 prescriptions being picked up. But we have
20 revamped our medication guide for opioids to a
21 one-page document that is intended to be friendly
22 to the patient. We've had a great group here of

1 communicators working on that and developing that
2 document. And there are other ways to try and
3 share that information. So it's in the label.
4 It's in the medication guide.

5 As part of the extended-release, long-acting
6 REMS, there's a patient information sheet. There's
7 a document that prescribers can use to help provide
8 additional information for patients, anything
9 specific. It's another opportunity there. But
10 we'll keep writing the labels in the hope that
11 someday people read them, but we will try and
12 pursue other avenues to get the messaging out.

13 DR. BROWN: Dr. Nelson, did you have a
14 comment?

15 DR. NELSON: Just quickly. I just
16 googled -- well searched "flush list" on the FDA
17 website, and it's there. And it specifically,
18 though, is limited to analgesics, which I think is
19 important to note because a lot of the negative
20 effects, in terms of the environment, are related
21 to things like antibiotics, contraceptives, various
22 issues. You read about fish being found that are

1 very odd are often related to that.

2 I would also mention that things like farm
3 pesticides and various products used in animal
4 husbandry, within the Chesapeake Bay watershed,
5 which is huge, including a large part of New York,
6 to our colleagues in New York, is an important
7 issue.

8 So I don't want people to over-generalize
9 flushing of medications to go beyond this
10 particular topic. And I know that wasn't Sharon's
11 intent, but one of my --

12 DR. FLICK: Skip, if you go to the EPA
13 website, there's not a word there, in their guide
14 on flushing. They don't say anything about
15 flushing being appropriate for --

16 DR. NELSON: Yes. But the EPA is obviously
17 under certain scrutiny to -- whatever. But we
18 won't go into that political issue.

19 (Laughter.)

20 DR. BROWN: What do you mean by that?

21 (Laughter.)

22 DR. BROWN: Dr. Tyler is on the phone and

1 has a question. Linda?

2 DR. TYLER: Yes, I had a couple of comments.
3 I think one thing that hasn't been mentioned, or
4 needs to be reiterated is the fact that we should
5 also emphasize what's the duration of therapy for
6 patients. And so there may be opportunities that
7 we don't prescribe as much. I mean, many people
8 described that they ended up with extra after an
9 injury. So do we rethink what the duration of
10 therapy that we should prescribe in the initial
11 prescriptions? And I think there are some
12 opportunities there.

13 I was also going to talk about the comment
14 about flushing. But I think one thing to
15 recognize, the DEA only loosened up the
16 regulations, so to speak, to allow for many
17 pharmacies to have takeback bins in the last two
18 years.

19 So I think it's working with communities to
20 enable pharmacies to have takeback programs so that
21 they are able to do it, because that's obviously
22 the safest way to dispose of medications, and it's

1 a message that we can say for all medications, use
2 the takeback bins. So I think they've been pretty
3 successful. I know Washington is one of the states
4 that has really had the public messages around
5 this.

6 I think the other comment I wanted to make
7 is we had an earlier advisory committee where we
8 spent a lot of time talking about should educating
9 providers be something that we should do. I think
10 we've brought up many issues today about what's
11 unique in these drugs in pediatrics that it's worth
12 incorporating in those programs as we develop them,
13 and not automatically assume people know that
14 there's all the things that we talked about that
15 are unique to pediatrics in the different age
16 groups, the different drug products. I think we
17 have some opportunities to combine it there.

18 I mean, a lot of us have talked about
19 different things where we have the opportunity to
20 partner with other agencies, other groups that are
21 also developing guidelines, and developing
22 consistent messages.

1 DR. BROWN: Thank you, Linda.

2 Dr. Higgins?

3 DR. HIGGINS: This is to Dr. Lasky's
4 question, or her point about not hearing much about
5 the patient experience. But I want to just share
6 with you that my son was born with bilateral club
7 feet, and I am so grateful for the pain management
8 that he had. And to see that there are some
9 physicians out there that think pain medicine is
10 not necessary was shocking to me as a parent of a
11 child like that.

12 DR. BROWN: Dr. Hoehn?

13 DR. HOEHN: Just to go back to the whole
14 disposal flushing thing, we were just reviewing the
15 list available online, and I still think it's not
16 as clear-cut as people might think it is. Because
17 for methylphenidate, it says you can flush the
18 patches but not the pills. So I just think it's
19 still not super clear what can go where.

20 DR. HERTZ: Well, all of the opioid
21 analgesics can be flushed according to our
22 labeling. The older immediate-release products are

1 may be silent on them, but we're working on that
2 effort now. All of the extended release have that,
3 and the medication guide for the extended release
4 has it, and the IR new medication guide will have
5 it.

6 So hopefully those two efforts, the labeling
7 effort that's going on now, which will get the
8 immediate-release product labels up-to-date, and
9 we'll provide medication guides for those products
10 as well, will be able to clearly deliver that
11 message.

12 DR. HOEHN: So you're saying things such as
13 methylphenidate pills could be flushed, even though
14 they're not on the pill, they're just not listed on
15 the label because they're old?

16 DR. HERTZ: I'm not mentioning
17 methylphenidate. I'm only talking about the opioid
18 analgesics.

19 DR. HOEHN: I'm only saying because
20 methylphenidate is on the list.

21 DR. HERTZ: I know. I don't what the
22 considerations were for the drug groups outside of

1 my group.

2 DR. HOEHN: Got it.

3 DR. HERTZ: So I could look into it just on
4 a side basis for you to find out why, but for the
5 opioid analgesics --

6 DR. HOEHN: Right.

7 DR. HERTZ: -- we are pretty consistent and
8 pretty clear on safe disposal of those products.
9 And we've even gone so far with some of the higher
10 potency fentanyl products, that are indicated for
11 breakthrough cancer pain, to require that the
12 companies create some additional safeguards
13 regarding disposal in that setting.

14 But for the oral products that are typically
15 administered to children, and most of the products
16 that are consumed by adults for managing pain,
17 those are suitable for flushing according to our
18 analyses and the flush list.

19 DR. HOEHN: Yes. Then I don't know if it's
20 a question for Dr. Nelson, because it's something
21 we talked about yesterday, not just with narcotics
22 but with the adolescent substance abuse population.

1 And certainly ADHD meds and things like that are a
2 huge risk for teenagers and things like that. So
3 that's why I was thinking along the lines of
4 substance abuse, not just opioids.

5 DR. BROWN: Dr. Hudak? Dr. Neville?

6 DR. NEVILLE: Mine is just a quick comment,
7 because I agree with Dr. Hertz. And before, years
8 ago, I did a sabbatical here. I don't read the
9 label either. So maybe it's a communication issue,
10 and I know maybe it's beyond purview of FDA, but I
11 know FDA also has a strong communications
12 department, and maybe it's as simple as a public
13 service announcement.

14 I mean the government does that all the
15 time. And it's now well known in the media and the
16 government that opioids are a problem, so why isn't
17 there a public service announcement about flushing
18 or getting rid of them and the dangers of them
19 sitting in the medicine cabinet? And I'm sure AAP
20 would be happy to help with that.

21 DR. BROWN: Dr. Draker?

22 DR. DRAKER: My bias is obviously towards

1 education of prescribers. The children don't get
2 the medicine unless we prescribe it. To that end,
3 and not meaning to advocate for New York State, but
4 in July, New York State implemented an initial
5 acute 7-day only prescription policy for opioid
6 medications. You can refill it after that if you
7 demonstrate evidence of chronic or continued pain,
8 but as for initial prescriptions, they only allow a
9 7-day prescription.

10 DR. BROWN: Any other comments?

11 (No response.)

12 DR. BROWN: If there are no other comments
13 from the group, I'd like to end by saying that this
14 has been a phenomenal discussion, and I personally
15 appreciate every single one of you folks for making
16 time out of your schedule. We've really been
17 looking forward to having this discussion for a
18 long time.

19 One of the things that is imperative, and I
20 think that we know this as pediatric healthcare
21 providers, is that it's really imperative to
22 provide the safest healthcare for children. And

1 I've taken to heart what Dr. Nelson recounted
2 yesterday about the issue of having children
3 involved in research versus the historical issue of
4 protecting them from research. And I hope that
5 some of the discussions that we've had over the
6 last two days have convinced most that even if this
7 is difficult, that it is something that really
8 needs to be done for this special class of drugs.

9 We're going to be using opioids for the
10 foreseeable future. I don't see any way around
11 that. So learning, continuing after 4,000 years of
12 use, continuing to learn what is the best way to
13 use these compounds, and the safe way to use them,
14 is incumbent on all of us that take care of
15 children.

16 My summary for question 6 is data, data,
17 data, data, data. And with that, I will say data.

18 (Laughter.)

19 DR. BROWN: And I would ask the question,
20 what can we do to help? How can we implore our
21 congressmen? Who can we talk to? How can we
22 provide assistance to get done what needs to be

1 done? This is a historical problem, and you've got
2 50 people, 35 or 70 people around this table, all
3 of whom have said the same thing. And I think
4 probably all of them want to come and live with you
5 guys and help.

6 I think we talked about, in terms of
7 question 6, expanding the CDC guidelines to
8 children less than age 18. And I know there's been
9 discussions within and between the CDC and the FDA
10 about the advisability of some of the issues around
11 the guidelines. But that said, I think that if
12 they're going to be guidelines out of there, and
13 they're going to be supported by our federal
14 government, that children should be a part of
15 those.

16 There are several other issues that were
17 discussed. We talk about whether or not we know
18 the correct duration of therapy for some of the
19 reasons that we are using opioids, whether we know
20 the correct dose. And we also talked about adding
21 pediatric information to our current REMS programs,
22 which I think is a great opportunity for us. And

1 by the way, Dr. Hertz, I'll be glad to write that,
2 and the cost will be nil.

3 Last I'll say that all of the opioid
4 compounds that are known in this universe can be
5 flushed.

6 (Laughter.)

7 DR. BROWN: Are there any other comments
8 before we ask Dr. Hertz to finish up for us?

9 (No response.)

10 DR. BROWN: Dr. Hertz?

11 DR. HERTZ: Thank you again for your time
12 and effort. I think it's just clear how
13 challenging the many different aspects of
14 addressing the needs for information about
15 pediatric analgesics, just how complex that issue
16 is. So thank you for your time and thoughts, and
17 we appreciate it.

18 DR. BROWN: Panel members, please take all
19 your personal belongings with you as the room is
20 cleaned at the end of the day. All materials left
21 on the table will be disposed of. Anybody left in
22 the seats will be disposed of.

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(Laughter.)

Adjournment

DR. BROWN: Please also remember to drop your name badges at the registration table. We'll now adjourn this meeting. Thank you for coming.

(Whereupon, at 2:39 p.m., the meeting was adjourned.)