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

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C O N T E N T S

P R O C E E D I N G S

(8:07 a.m.)

Call to Order

Introduction of Committees

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BATEMAN: Brian Bateman,

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

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

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

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

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

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

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

George Washington University, and I'm a consultant.

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

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

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

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

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

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

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

DR. CATALETTO: Mary Cataletto. I'm a

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

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

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

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

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

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

Committee.

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

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

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

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

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

to help us with some very important topics.

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is

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

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

Conflict of Interest Statement

DR. BEGANSKY: Thank you.

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

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

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

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

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

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

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

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

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting

members to disclose any public statements that they have made concerning the topic at issue. Dr. Bridgette Jones is participating in this meeting as the health care representative, and that is a non-voting position.

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

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

Dr. Steven Weissman has acknowledged that he

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

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

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

FDA Introductory Remarks - Sharon Hertz

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

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

We have gotten information about the

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

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

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

present.

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

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

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

DR. BROWN: Thank you, Dr. Hertz.

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

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

transfusion medicine, Syracuse, New York.

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

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

Clarifying Questions

DR. BROWN: Thank you, Linda.

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

Dr. Patrick?

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

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

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

(No response.)

Open Public Hearing

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

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

Likewise, the FDA encourages you, at the

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

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

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

DR. MALVIYA: Good morning. My name is

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

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

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

Prescription opioid abuse has impacted the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

the welfare of children.

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

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

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

The Code of Federal Regulations, 21 CFR 56,

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

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

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

intervention.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

At the same time, the FDA labeled OxyContin

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

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

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

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

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

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

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

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

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

treatment of chronic pain, including conducting studies in children.

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

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

DR. BROWN: Thank you, Mr. Thompson.

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

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

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

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

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

data from healthcare claims databases and electronic medical records.

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

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

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

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

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

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

safety.

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

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

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

results.

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

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

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

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

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

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

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

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

Children with cancer related pain are

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

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

There are challenges in site recruitment as

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

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

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

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

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

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

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

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

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

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

There is no evidence that providing

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

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

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

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

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

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

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

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

DR. BROWN: Thank you, Dr. Houck.

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

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

Charge to the Committee - Sharon Hertz

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

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

Questions to the Committee and Discussion

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

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

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

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

Is that question clear to the members of the panel?

(No response.)

DR. BROWN: Response. Dr. Walco?

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

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

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

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

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

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

alone.

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

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

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

DR. BROWN: I know in discussions with

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

DR. WALCO: I alluded to it yesterday. I think the tragedy is that -- you've heard about the CDC guidelines. In the second paragraph of those guidelines it states outright that anybody under 18, the guidelines do not pertain to them. And I think there's some profound risk of extrapolating or generalizing those recommendations to children without really understanding the issues. Similarly, the National Pain Strategy was released through HHS in March, and children were completely neglected from that.

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

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

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

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

DR. BROWN: If you could just --

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

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

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

DR. BROWN: Dr. Ruha?

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

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

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

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

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

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

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

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

DR. BROWN: Dr. White?

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Patrick?

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

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

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

DR. BROWN: Dr. Czaja?

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

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

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

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

DR. BROWN: Dr. Hoehn?

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

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

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

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

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

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

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

DR. BROWN: Dr. Gerhard?

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

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

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

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

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

DR. BROWN: Dr. Cnaan?

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

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

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

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

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

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

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

DR. BROWN: Dr. Neville?

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

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

most.

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

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

DR. BROWN: Dr. Jones?

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

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

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

DR. BROWN: Dr. Wade?

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

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

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

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

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

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

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

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

neonates or premature babies at all.

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

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

DR. BROWN: Dr. Flick?

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

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

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

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

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

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

Dr. Kibbe?

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

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

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

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

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

The study design for a prospective study is

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

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

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

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

DR. BROWN: Thank you, Dr. Kibbe.

Dr. Bateman?

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

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

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

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

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

DR. BROWN: Dr. Higgins?

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

DR. BROWN: Dr. Havens?

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

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

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

DR. BROWN: Dr. Shoben?

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

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

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

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

DR. BROWN: Dr. Czaja?

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

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

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

DR. BROWN: Dr. Neville?

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

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

DR. BROWN: Dr. Hertz?

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

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

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

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

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

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

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

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

the environment in which we're having this meeting.

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

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

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

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

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

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

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

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

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

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

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

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

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

So, given that, yes, but that's the kind of thing. So what do you think we need to do? Dr. Levy provided background for why adolescents may be at greater risk, and she mentioned one study, that she had some others that she could send us.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

So it might be safety profiles even beyond

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

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

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

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

DR. BROWN: Dr. Ruha?

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

(Laughter.)

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

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

DR. BROWN: Dr. Hertz, go.

DR. HERTZ: Yes.

(Laughter.)

DR. BROWN: Dr. Patrick?

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

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

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

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

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

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

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

DR. BROWN: Dr. Turer?

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

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

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

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

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

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

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

ratios.

DR. BROWN: Dr. Kaye?

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

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

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

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

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

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

DR. BROWN: Dr. Bateman?

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

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

DR. BROWN: Dr. Walco?

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

It sounds to me from the discussions we've

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

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

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

DR. BROWN: Dr. Lasky?

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

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

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

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

DR. BROWN: Dr. Hoehn?

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Neville?

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

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

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Harralson?

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

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

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

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

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

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

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

DR. BROWN: Thank you, Dr. Tyler.

Dr. McCann?

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

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

DR. BROWN: Dr. Maxwell?

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

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

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

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

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

DR. BROWN: Dr. White?

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Havens?

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

The premature infants have a different

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

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

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

hypersensitivity, as we heard from before.

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

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

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

So I appreciate the specificity of your

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

DR. BROWN: Dr. Hudak?

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

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

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

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

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

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

study.

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

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

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

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

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

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

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

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

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

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

Another thing that was made very clear is

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

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

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

groups who have chronic pain.

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

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

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

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

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

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

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

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

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

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

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

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

(No response.)

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

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

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

(Laughter.)

DR. BROWN: Just kidding.

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

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

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

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

Is that question clear to the panel?

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

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

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

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

DR. BROWN: Dr. Emala?

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

DR. BROWN: Dr. Emala?

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

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

DR. BROWN: Dr. Gupta?

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

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

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

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

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

I think some of those screening assessments

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

DR. BROWN: Dr. Havens?

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

DR. BROWN: Dr. Lasky?

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

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

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

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

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

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

DR. BROWN: Dr. Nelson?

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

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

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

DR. BROWN: Dr. Kaye?

(Dr. Kaye gestures no question.)

DR. BROWN: Dr. Bateman?

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

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

their considerable risks, are absolutely indicated will be important.

DR. BROWN: Dr. Ruha?

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

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

more.

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

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

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

Can we move on to question number 3? Question number 3 is, studies of immediate-release opioid analgesics are generally conducted in patients with acute painful conditions, including post-operative pain, as well as traumatic or other painful conditions, that require opioid analgesia and are expected to be of relatively short duration.

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

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

The agency is asking the committee to

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

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

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

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

bring that up.

DR. BROWN: Comments? Dr. Patrick?

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

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

DR. BROWN: Dr. Walco?

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

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

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

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

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

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

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

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

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

So I guess those would be the two starting

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

DR. BROWN: Dr. Havens?

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

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

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

DR. BROWN: Dr. Neville?

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

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

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

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

DR. BROWN: Dr. White?

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

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

might be approached as well.

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

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

DR. BROWN: Dr. Hoehn?

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

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

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

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

DR. BROWN: For our FDA colleagues, we need

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

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

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

Are we on the right track?

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

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

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Lasky?

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

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

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Wade?

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

DR. BROWN: Dr. White?

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

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

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

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

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

DR. BROWN: Thank you, Dr. White.

Dr. Patrick?

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

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

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

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

DR. PATRICK: Thank you, sir.

DR. BROWN: Any other comments?

(No response.)

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

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

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

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

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

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

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.

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

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

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

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

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

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

DR. BROWN: Comments? Dr. Kibbe?

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

common disease.

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

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

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

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

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

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

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

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

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

All right. Now you can start to extrapolate

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

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

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

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

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

DR. BROWN: Any response?

DR. HIGGINS: That's excellent.

UNIDENTIFIED MALE: Sorry. Could you repeat that?

(Laughter.)

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

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

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

the pain has started again.

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

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

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

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

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

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

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

information or whatever you have.

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

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

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

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

DR. KIBBE: Right.

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

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

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

DR. BROWN: Dr. Walco?

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Ruha?

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

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

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

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

DR. BROWN: Dr. Cnaan?

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

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

the base study within that framework.

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

DR. BROWN: Dr. Maldonado?

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

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

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

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

DR. BROWN: Dr. Havens?

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

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

So is this a question about how to scale

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

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

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

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

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

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

Is that part of the question?

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

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

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

DR. HAVENS: [Inaudible - off mic].

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Nelson?

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

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

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

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

willingness to extrapolate efficacy.

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

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

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

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

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

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

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

adolescent.

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

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

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

outcome.

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

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

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

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

DR. BROWN: Dr. Lasky?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. BROWN: Dr. Czaja?

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

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

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

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

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

DR. BROWN: Dr. White?

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

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

DR. WHITE: Okay.

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

concurrent medications; and individual variability in general.

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

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

than a 25-weeker, but still challenging.

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

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

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

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

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

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

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

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

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

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

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

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

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

Does that make any reasonable sense?

DR. HERTZ: Sure.

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

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

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

Dr. Kibbe?

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

Minimum effective concentration, as

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

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

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

impaired renal function.

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

DR. BROWN: Dr. Harralson?

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

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

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

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

DR. BROWN: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. Well, as a

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

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

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

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

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

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

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

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

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

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

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

about that for many products.

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

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

DR. FLICK: Okay.

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

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

DR. NELSON: Skip Nelson. I would just

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

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

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

DR. BROWN: Any other comments?

(No response.)

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

(Laughter.)

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

But if it occurs, it may follow that a safe starting dose by using experienced dosing trial based on the history of use -- in other words, rather than having an efficacy trial, going to establishing a safe starting dose from historical data, and then requiring efficacy data if that data was found to be incomplete.

The examination of data relating to these drugs is difficult, will need to examined in a unique way, and may combine the use of known data for starting doses and extrapolation to other populations. Obviously we've spoken a lot about

the fact that the pediatric population is very granular. So the matrix, as Dr. Kibbe calls it, will have a lot of cells.

Opioids, however, may be a special case, that extrapolation doesn't fit for all patients for all drugs, and that's obvious from the question. For those indications, may need more complete data and larger studies. And as we've just heard, there's some sense that those larger efficacy studies, if they're done, may need to be done in an inpatient setting in post-surgical patients.

Does that capture a little bit of what anybody thought that we said?

(No response.)

DR. BROWN: Let's move on to question number 5. And question number 5 for discussion, you have heard about significant challenges associated with the study of opioid analgesics in pediatric patients. Discuss possible approaches to overcome these challenges.

Is that clear? Is that question clear to everyone? Is that a question that we can answer?

Any comments or questions? Dr. Patrick?

DR. PATRICK: Just a couple quick things to reiterate. Partnering with other organizations to gather some of these secondary data, including the Children's Hospitals of America, where a large proportion of our complex children are taking care of, there are claims data that are linked to medications. And that may be a useful source as well as the other things we've discussed, the Neonatal Network, as well as Vermont Oxford Network.

DR. BROWN: Dr. Higgins?

DR. HIGGINS: One particular challenge that I've heard a lot about in the last couple days is the enrollment or recruitment for pediatric trials, and this is something that I find particularly frustrating. I used to be a patient recruiter for Alzheimer's trials, as well as other neurological diseases, and worked tirelessly to get guardians or caregivers to sign on to these trials.

It was a real challenge, but I think with the right educational campaign, if there was such a

thing, to have an educational campaign educating parents about the benefits of trial participation, I think we'd go a long way in boosting those enrollment rates.

DR. BROWN: Dr. Turer?

DR. TURER: Thank you. Christy Turer. So one thing that I thought about is, there are certain conditions that absolutely warrant opioids. And then the question really is, what is the starting dose that is needed, and what is the correct duration of use? So, that's one pot of conditions.

Another one that is less clear are conditions in which it's controversial whether opioids are really needed. So for example, fracture, particularly in adolescents who are going to be prone to them either because of football or because of other athletic issues, who would be at greater risk for abuse potential in that developmental period.

Could there be a role for randomized trials where we randomize people who have, let's say, risk

fractures or arm fractures? Not so much femur. I mean, some of these are clearly, that would warrant stronger pain medication. But then randomize people to either getting NSAID versus opioid Tylenol, or just Tylenol alone, and see, do we actually need opioid. Because maybe the starting dose in certain populations of opioid is zero, and I think that would be really meaningful in a population that's at great risk.

DR. BROWN: One way to do that, rather than giving no opioid, would be to use -- and folks have done this in the past, look at opioid sparing by giving -- and we've spoken quite a bit about multimodal therapy, and I think that's what people have been trying to get at.

Dr. Emala?

DR. EMALA: I see one of the major challenges of accomplishing a lot of what's been discussed over the last two days is funding these types of studies. So we've I think had unanimous agreement of the need for more data, and a lot of granular discussion about what types of studies

might be warranted. But some frustration discussed yesterday where investigator-initiated studies that are submitted to the NIH are not very well received.

I think there's also some frustration sometimes when priorities of one federal agency don't get transmitted to another, imperatives such as this for the FDA being conveyed to the respective institutes of the NIH.

So I think it would be a very important component of getting over these challenges for the FDA to be working in concert with the NIH, minimally at an RFA type of approach, if not a U19 type of approach, because I think, although the vast majority of NIH research is funded by investigator initiated studies, that often falls on the deaf ears of uninformed study sections; whereas if there's actually a call for applications, an RFA or a U19 mechanism, I think the chance of having funding for these great plans, which will remain great plans without appropriate funding, will be incomplete.

Secondly, I think in our background information, we read a little bit about the responsibility of industry and industry funding for these types of studies in pediatric pain populations. And there apparently is already an initiative where industry is incentivized to invest in these types of studies by having the exclusivity of their products extended for a period of six months.

So I wonder if that's enough of an incentive to have industry fully vested in funding these types of studies, or whether even a REMS type of program that's the responsibility of industry to fund could be incorporated. But I think at the end of the day, great plans will remain great plans unless there are active efforts at the federal level to have these types of studies funded.

DR. HERTZ: I just want to correct one little thing, because sometimes things can snowball a little bit. REMS authority doesn't really give us the opportunity to require the kinds of efficacy studies, development studies that we've been

talking about.

The authority we have to require that of industry would come under the pediatric legislation that you've heard about, PRE, where we can require it for the product in the indication, or BPCA, if they want to seek pediatric exclusivity, and then we study the moiety across all relevant uses.

So the REMS is about safety features necessary for maintaining the risk balance as opposed to gaining this type of new study. So I just wanted to clarify that.

DR. EMALA: I wasn't suggesting that this would be appropriate in a REMS program, I was just curious if analogous types of obligations could be extended to industry like the REMS program was.

DR. BROWN: Dr. Draker?

DR. DRAKER: Bob Draker. Does the FDA have any access to the I-STOP data available in certain states? Only because in New York State, we see a lot of that information that would be very valuable at the state level with regards to getting demographics on who the prescribers are, the age

groups and the locations of the recipients. Some states have that, but that really gives you quite a bit of information with regards to prescriber practice, and the approaches taken for certain diagnoses as well.

DR. HERTZ: Can you restate the name of that database?

DR. DRAKER: It's called I-STOP, which --

DR. HERTZ: I-STOP.

DR. DRAKER: -- is through the DEA. Some states have adopted I-STOP. It's where you call in. Any time you're going to use a controlled substance, you register the particular patient. And the database, the statewide database, allows you to look at -- or the state does, to look at information with regards to the number of prescriptions, when they were filled, who they were prescribed by.

DR. NELSON: Skip Nelson. My understanding is that many of those programs are voluntary; at least where I have my license, I got an email saying do you want to participate. But obviously

I'm not prescribing these being at FDA, but my impression was, it was a voluntary program, which would undermine the quality of the data.

DR. DRAKER: That program is not voluntary; it's mandated in New York State.

DR. NELSON: Well maybe in New York, but not in my state.

DR. BROWN: Yes. This varies state by state. There are still a few states that are not requiring that. But you're correct that there are lots of states that do require that. For example, in a state like Kentucky, where we have a big drug problem, it's been very useful in helping us change the behavior of both physicians and patients.

DR. DRAKER: In New York State alone, there's been a tremendous decrease, in the two years that this has been very active, in the use of opioid and other controlled substances.

DR. BROWN: Dr. Walco? Dr. Crawford?

DR. CRAWFORD: Thank you. Stephanie Crawford. To pick up a little on what Dr. Emala was stating in terms of a lot of the issues

yesterday, especially that were raised with the funding, and it has been stated a lot today that the condition of pain does not affect only monolithic cohorts; it's so widespread. So maybe in terms of those who are looking at conducting studies, expanding the potential funding sources, either from FDA or in add on with others, or just other funding mechanisms.

For example, it could be -- some research questions very focused could possibly be add-on questions with respect to rare disease research funding mechanisms for a certain, for example, pediatric cancers or sickle cell or Ehlers-Danlos. It's just many diseases, but it might be a different way. And maybe one of FDA's roles could be consideration of one or two, three focused research questions that could be part of any such study in any co-funded area.

One of the issues for me that's always of interest with any research studies is, if we go back to the ethics talks, distributive justice, fair distribution of the benefits of the study as

well as the burdens.

Oftentimes, we'll see excellent studies that are conducted, but they may be only for patients in a low-income, urban setting, or extraordinarily affluent suburban settings, or observational studies that are Medicaid only or commercially insured only for covered individuals.

So I would just ask that there be encouragement of any pediatric studies in this area that will look at a wide mix of patients.

DR. BROWN: Dr. Neville?

DR. NEVILLE: Similar to that, I'm sitting here thinking, wondering if there is a way to leverage BPCA, because none of the older opiates, at least to my knowledge, are on the desired drug list. And I understand funding, even for BPCA, is an issue, but I can say we were somewhat successful with hydroxyurea, an old drug that no sponsor really was interested in because it was off patent. And there may be some way to pull it all together with NIH through that mechanism, at least for some of the older drugs.

DR. BROWN: Dr. Patrick, did you have -- are there any other comments surrounding this question about the possible approaches to the challenges that have been identified?

(No response.)

DR. BROWN: If not, some of the challenges that we've heard over the last two days relate to many things, but largely about two things, funding and fear. I think it's been identified that the NIH is a possible source of funding. I haven't heard anybody suggest a larger group that might be more useful. I think there are other data sources, but for a source of dollars to provide to individual or groups to get these studies done, the NIH seems to be the natural source.

In terms of fear, fear for your career if you do these studies, fear of hurting somebody, I think the AAP again, I said this yesterday, could be very helpful because this is a marketing issue. And I don't think that the FDA can probably be, at least in part, involved with this. And currently the FDA and the AAP have a good working

relationship, so that they could market the need for these studies to be done.

In terms of getting to some of the specifics of the challenges, identifying data sources, and we've heard about a variety of different data sources and consortia that might be used. One of particular interest would be the Oxford data source. I suggested yesterday that Medicaid data might be able to be used to an advantage, as well as DEA data.

It was suggested that there needs to be some kind of education process around the need for these studies for all patients. And again, this is probably within the realm of the American Academy of Pediatrics.

When we talk about industry and how industry can be effective, over the course of the last two days I've been trying to think about what there is available to pull industry into this. And in reality, it all comes down to whether the extension of their license for drugs is incentive enough for industry to be involved, and it currently is not

apparent that it is. So at the very least, some thought needs to be given to rethink the incentives that industry currently has under PREA to get the studies done that are required.

Does that sum the group?

(No response.)

DR. BROWN: So let's go on to our last question. And the last question is, provide additional comments that you believe are important to address issues related to the use and study of opioid analgesics in pediatric patients.

Is that a question that we can answer?

(Laughter.)

DR. BROWN: Dr. Turer?

DR. TURER: I don't know if this is out of left field, but increasingly it seems that there are a lot of athletes talking about their issues with pain killer abuse. So in thinking about avenues of funding, it might be worthwhile to tap into the NBA, the NFL, and look for partners that are higher profile, especially adolescents. They may resonate with them some more. So outside of

the medical venue, but nevertheless, I think a potent source of influence.

DR. BROWN: Dr. Hertz, do you think that the FDA could partner with the NBA?

(Laughter.)

DR. BROWN: Or do you reject that out of hand?

DR. HERTZ: I'm going to head that committee.

(Laughter.)

DR. BROWN: I know there must be other comments. Dr. Crawford?

DR. CRAWFORD: It's a comment to send back to the group. I've heard several talk about the need for other education and the use, but I don't know the answer, but may I ask if the chair or any member of the committee could make more specific recommendations about how to increase education on appropriate prescribing and monitoring?

DR. BROWN: Well, the FDA through the REMS program certainly has a readily established organizational structure that requires almost all

of pharmaceutical industry now, who create individual opioid drugs, to create educational programs.

Now these programs, for the most part, are related to the prescriber, but I can see that could easily be extended to the patient. And I think some responsible pharmaceutical companies have already done that. We've talked about Accutane a lot. The program that was created for Accutane was created not by the FDA, but it was created by the industry that was responsible for putting Accutane on the market.

So industry is aware of the requirements, and they can do this. The question is, what kind of incentives are there that would be provided to do that. With the REMS program, the incentives are pretty stark. And in discussions that we had in May, unfortunately prescribers haven't really taken advantage of that. And I think that the FDA is working internally on changing things up so that that program will be more successful.

Other comments?

(No response.)

DR. BROWN: Dr. Flick?

DR. FLICK: Today the burning platform is opioid abuse, misuse, overdose, death. In the past, it was Accutane, or it's anesthetic-related neurotoxicity, which is still an issue. Tomorrow, in the future, it's going to be some other issue related to drugs or drug approval. And each time we sit around this table, the common theme is always, we don't really have the data.

It would seem to me that it would be far cheaper for both industry and government to come together in the era of big data. We have electronic health records that are linkable now. We have very large electronic health record databases at Kaiser. We have one. Optum has one. There are many others.

We could produce data, or a dataset, that is minable, so whenever these issues come up, we can go to that database to answer the question, rather than to approach each one of these issues as if they're separate issues and deal with them in a

piecemeal way, which is extremely inefficient, unsatisfying, and ultimately really expensive.

DR. BROWN: Thank you, Randy.

Dr. Hudak?

DR. HUDAK: Yes, one thought I had was -- and I'm not aware to what extent this may be occurring already, but the reference was made this morning by one speaker to the CDC's document they released in March as a public policy statement on opioids. And there were 12 specific recommendations in that document. It was a very thoughtful document, very well researched. And to the extent that some of these recommendations might be able to be applied by FDA at the class level to these opioids, that might be something the FDA would want to certainly carefully consider.

DR. BROWN: Now, are you speaking of expanding the CDC guidelines, which are not operative below age 18, I believe, to the pediatric age group?

DR. HUDAK: So, yes. I think some of these things can be expanded by extrapolation certainly

to some pediatric age groups. So I think that's something the FDA could take a look at and consider. Certainly not all of these recommendations belong in labeling, but I think there are at least a couple that provide additional information that would be helpful on the labeling.

DR. BROWN: Dr. Shoben?

DR. SHOBEN: Yes, so I just wanted to state for the record, one of the challenges I see is the lack of good outcome data, particularly in younger pediatric patients. So it's very easy in opioid efficacy studies in adults that you have this very nice patient report outcome about their pain. And that probably works fine for adolescents because they can also report on their pain very straightforwardly.

It would be really nice if there was a really good way to measure it. We've talked about this a little bit in various comments, but I just wanted to state that for the record and say that it's really challenging to come up with novel trial designs and better statistics and things without a

good outcome measurement.

DR. BROWN: Dr. Bateman?

DR. BATEMAN: I think we'd all agree that left over medications that are not properly disposed of that are put in the medicine cabinet are an important source of opioids that end up being misused or diverted. And I think part of the solution to that is having prescribers prescribe in a more judicious fashion, giving out a fewer days' supply, or a supply that's titrated to what the patients are actually going to use.

But another important component is just having the patients throw away the leftover medication. And what I found talking to patients and other providers, is there's a lot of confusion about how to do that. And I guess the label that FDA has put on opioids suggest that they can be flushed, but I don't think that message has really gotten out there.

So I think that to the extent that FDA can increase the awareness that these medications can be flushed, and can encourage providers to educate

their patients about the need to do that, I think that would potentially be an important step in reducing the reservoir of these medications available for misuse.

DR. BROWN: Dr. Lasky?

DR. LASKY: I realize as we're wrapping things up, we do have a member of the committee who is representing the patient voice, but we haven't thought very much -- talked about the role of the patient, the parents, and children as partners. And there's a lot of different aspects of it, particularly if we're talking about trying to get funding through Congress or wherever else.

But there's a specific role, and I'm not up to date on, and for Dr. Hertz, I know FDA is doing a lot in terms of patient preferences and how this could play into this area in terms of studies of opioids in kids. However it is, that's an area that would be good to explore and encourage.

DR. BROWN: Dr. Jones?

DR. JONES: My comments are really along the same lines. I think this is really a public health

problem that a lot of people aren't aware of, especially parents. So most parents probably don't know that we don't really know the effective and safe dose of an opioid to give their child, they just assume that we are giving them the right dose and that it's been studied. So I think engaging the public in this problem would be important.

I'm an allergist, and we've all heard about the EpiPen pricing. And I think one of the reasons why we've heard of that is because everybody knows you don't mess with food allergy patients, because those parents will come out, and they will get you.

(Laughter.)

DR. JONES: So I think using some of those same approaches in engaging the families and the patients that this actually affects is important. So if the FDA could partner with the AAP, partner with parent organizations for sickle cell, pediatric cancers, and really get the word out about these are the problems that we're having with studying these medications and can you help us with solving some of these problems, I think that would

make somewhat of an impact.

DR. BROWN: Dr. Nelson?

DR. NELSON: I just wanted to ask a point of clarification from I believe Dr. Bateman. You said that medications can be flushed. I guess I've always thought that it would contaminate the water, and kill the fish, and all that kind of stuff.

Could you expand on that, please?

DR. BATEMAN: Dr. Hertz, can you help me out?

(Laughter.)

DR. HERTZ: So, you may be interested to know that we actually maintain a flush list here at FDA, in conjunction with some other agencies, because we don't want to put certain products into the water supply, if it can be avoided. Part of how we decide what should be on a flush list is in part based on risk. And having opioids discarded in the trash or someplace where there could be accidental exposure or theft is a concern.

When water quality is assessed, opioids are generally not on the list of things that are being

detected. So it doesn't seem that we're creating too much of a problem, although I'm not sure how many people are listening to that. But the products that we're talking about here, the schedule 2 and 3s, are all labeled for disposal by flushing, because that is a very secure way to get them out of the house, out of the reach of unintentional or intentional exposures.

There are also -- I believe it came out of ONDCP, the Office of National Drug Control Policy -- other recommendations for disposing of controlled substances, which include mixing them with kitty litter or coffee grounds, and securing them in a container in the trash, so making them unappealing and disposing of them in a container. So those are two ways that are possible.

Taking advantage takeback programs is another good one, and I know there are more of those than there had been in the past. We certainly support that as well. Some localities will accept controlled substances at local law enforcement offices. So I would check ahead before

showing up at your local police department with a bag full of something, but that is something that we've heard about as well.

So I think that you can consider -- depending on the amount and the frequency, certainly we think flushing is the best way to get them out of the chain of problems until we have better options for other types of takeback or send back programs.

DR. NELSON: I just might add to that, I guess I consider myself to be pretty responsible when it comes to that, and I've asked the pharmacist and all that. I've never heard that before. So perhaps to go along with patient education, that might -- and education of the pharmacists. I ask all the time. I have every medication since, you know for the last 18 years, at my house. So that might be something that you could add, patient education, when it comes to that.

DR. HERTZ: So I'll just bemoan the fact that it's in our labeling, and I would like to add

for general consumption that people should please read the labels. We spend a remarkable amount of time trying to make sure that the information in the labels is relevant and as up-to-date as possible. We've been engaging in a number of class labeling efforts to try and improve the information in general and improve the consistency of delivery.

We've done a lot of work on the extended and long-acting opioids. We are currently working on the immediate-release opioids, which is a much broader and older group of products. And I can tell you, it's taking quite a bit of resources to do this. But part of that will be to make sure that they all have disposal instructions, which will include, for this group, flushing.

I believe it's on our current medication guide. I know that they're not always delivered the way they're supposed to be at the time of prescriptions being picked up. But we have revamped our medication guide for opioids to a one-page document that is intended to be friendly to the patient. We've had a great group here of

communicators working on that and developing that document. And there are other ways to try and share that information. So it's in the label. It's in the medication guide.

As part of the extended-release, long-acting REMS, there's a patient information sheet. There's a document that prescribers can use to help provide additional information for patients, anything specific. It's another opportunity there. But we'll keep writing the labels in the hope that someday people read them, but we will try and pursue other avenues to get the messaging out.

DR. BROWN: Dr. Nelson, did you have a comment?

DR. NELSON: Just quickly. I just googled -- well searched "flush list" on the FDA website, and it's there. And it specifically, though, is limited to analgesics, which I think is important to note because a lot of the negative effects, in terms of the environment, are related to things like antibiotics, contraceptives, various issues. You read about fish being found that are

very odd are often related to that.

I would also mention that things like farm pesticides and various products used in animal husbandry, within the Chesapeake Bay watershed, which is huge, including a large part of New York, to our colleagues in New York, is an important issue.

So I don't want people to over-generalize flushing of medications to go beyond this particular topic. And I know that wasn't Sharon's intent, but one of my --

DR. FLICK: Skip, if you go to the EPA website, there's not a word there, in their guide on flushing. They don't say anything about flushing being appropriate for --

DR. NELSON: Yes. But the EPA is obviously under certain scrutiny to -- whatever. But we won't go into that political issue.

(Laughter.)

DR. BROWN: What do you mean by that?

(Laughter.)

DR. BROWN: Dr. Tyler is on the phone and

has a question. Linda?

DR. TYLER: Yes, I had a couple of comments. I think one thing that hasn't been mentioned, or needs to be reiterated is the fact that we should also emphasize what's the duration of therapy for patients. And so there may be opportunities that we don't prescribe as much. I mean, many people described that they ended up with extra after an injury. So do we rethink what the duration of therapy that we should prescribe in the initial prescriptions? And I think there are some opportunities there.

I was also going to talk about the comment about flushing. But I think one thing to recognize, the DEA only loosened up the regulations, so to speak, to allow for many pharmacies to have takeback bins in the last two years.

So I think it's working with communities to enable pharmacies to have takeback programs so that they are able to do it, because that's obviously the safest way to dispose of medications, and it's

a message that we can say for all medications, use the takeback bins. So I think they've been pretty successful. I know Washington is one of the states that has really had the public messages around this.

I think the other comment I wanted to make is we had an earlier advisory committee where we spent a lot of time talking about should educating providers be something that we should do. I think we've brought up many issues today about what's unique in these drugs in pediatrics that it's worth incorporating in those programs as we develop them, and not automatically assume people know that there's all the things that we talked about that are unique to pediatrics in the different age groups, the different drug products. I think we have some opportunities to combine it there.

I mean, a lot of us have talked about different things where we have the opportunity to partner with other agencies, other groups that are also developing guidelines, and developing consistent messages.

DR. BROWN: Thank you, Linda.

Dr. Higgins?

DR. HIGGINS: This is to Dr. Lasky's question, or her point about not hearing much about the patient experience. But I want to just share with you that my son was born with bilateral club feet, and I am so grateful for the pain management that he had. And to see that there are some physicians out there that think pain medicine is not necessary was shocking to me as a parent of a child like that.

DR. BROWN: Dr. Hoehn?

DR. HOEHN: Just to go back to the whole disposal flushing thing, we were just reviewing the list available online, and I still think it's not as clear-cut as people might think it is. Because for methylphenidate, it says you can flush the patches but not the pills. So I just think it's still not super clear what can go where.

DR. HERTZ: Well, all of the opioid analgesics can be flushed according to our labeling. The older immediate-release products are

may be silent on them, but we're working on that effort now. All of the extended release have that, and the medication guide for the extended release has it, and the IR new medication guide will have it.

So hopefully those two efforts, the labeling effort that's going on now, which will get the immediate-release product labels up-to-date, and we'll provide medication guides for those products as well, will be able to clearly deliver that message.

DR. HOEHN: So you're saying things such as methylphenidate pills could be flushed, even though they're not on the pill, they're just not listed on the label because they're old?

DR. HERTZ: I'm not mentioning methylphenidate. I'm only talking about the opioid analgesics.

DR. HOEHN: I'm only saying because methylphenidate is on the list.

DR. HERTZ: I know. I don't what the considerations were for the drug groups outside of

my group.

DR. HOEHN: Got it.

DR. HERTZ: So I could look into it just on a side basis for you to find out why, but for the opioid analgesics --

DR. HOEHN: Right.

DR. HERTZ: -- we are pretty consistent and pretty clear on safe disposal of those products. And we've even gone so far with some of the higher potency fentanyl products, that are indicated for breakthrough cancer pain, to require that the companies create some additional safeguards regarding disposal in that setting.

But for the oral products that are typically administered to children, and most of the products that are consumed by adults for managing pain, those are suitable for flushing according to our analyses and the flush list.

DR. HOEHN: Yes. Then I don't know if it's a question for Dr. Nelson, because it's something we talked about yesterday, not just with narcotics but with the adolescent substance abuse population.

And certainly ADHD meds and things like that are a huge risk for teenagers and things like that. So that's why I was thinking along the lines of substance abuse, not just opioids.

DR. BROWN: Dr. Hudak? Dr. Neville?

DR. NEVILLE: Mine is just a quick comment, because I agree with Dr. Hertz. And before, years ago, I did a sabbatical here. I don't read the label either. So maybe it's a communication issue, and I know maybe it's beyond purview of FDA, but I know FDA also has a strong communications department, and maybe it's as simple as a public service announcement.

I mean the government does that all the time. And it's now well known in the media and the government that opioids are a problem, so why isn't there a public service announcement about flushing or getting rid of them and the dangers of them sitting in the medicine cabinet? And I'm sure AAP would be happy to help with that.

DR. BROWN: Dr. Draker?

DR. DRAKER: My bias is obviously towards

education of prescribers. The children don't get the medicine unless we prescribe it. To that end, and not meaning to advocate for New York State, but in July, New York State implemented an initial acute 7-day only prescription policy for opioid medications. You can refill it after that if you demonstrate evidence of chronic or continued pain, but as for initial prescriptions, they only allow a 7-day prescription.

DR. BROWN: Any other comments?

(No response.)

DR. BROWN: If there are no other comments from the group, I'd like to end by saying that this has been a phenomenal discussion, and I personally appreciate every single one of you folks for making time out of your schedule. We've really been looking forward to having this discussion for a long time.

One of the things that is imperative, and I think that we know this as pediatric healthcare providers, is that it's really imperative to provide the safest healthcare for children. And

I've taken to heart what Dr. Nelson recounted yesterday about the issue of having children involved in research versus the historical issue of protecting them from research. And I hope that some of the discussions that we've had over the last two days have convinced most that even if this is difficult, that it is something that really needs to be done for this special class of drugs.

We're going to be using opioids for the foreseeable future. I don't see any way around that. So learning, continuing after 4,000 years of use, continuing to learn what is the best way to use these compounds, and the safe way to use them, is incumbent on all of us that take care of children.

My summary for question 6 is data, data, data, data, data. And with that, I will say data.

(Laughter.)

DR. BROWN: And I would ask the question, what can we do to help? How can we implore our congressmen? Who can we talk to? How can we provide assistance to get done what needs to be

done? This is a historical problem, and you've got 50 people, 35 or 70 people around this table, all of whom have said the same thing. And I think probably all of them want to come and live with you guys and help.

I think we talked about, in terms of question 6, expanding the CDC guidelines to children less than age 18. And I know there's been discussions within and between the CDC and the FDA about the advisability of some of the issues around the guidelines. But that said, I think that if they're going to be guidelines out of there, and they're going to be supported by our federal government, that children should be a part of those.

There are several other issues that were discussed. We talk about whether or not we know the correct duration of therapy for some of the reasons that we are using opioids, whether we know the correct dose. And we also talked about adding pediatric information to our current REMS programs, which I think is a great opportunity for us. And

by the way, Dr. Hertz, I'll be glad to write that, and the cost will be nil.

Last I'll say that all of the opioid compounds that are known in this universe can be flushed.

(Laughter.)

DR. BROWN: Are there any other comments before we ask Dr. Hertz to finish up for us?

(No response.)

DR. BROWN: Dr. Hertz?

DR. HERTZ: Thank you again for your time and effort. I think it's just clear how challenging the many different aspects of addressing the needs for information about pediatric analgesics, just how complex that issue is. So thank you for your time and thoughts, and we appreciate it.

DR. BROWN: Panel members, please take all your personal belongings with you as the room is cleaned at the end of the day. All materials left on the table will be disposed of. Anybody left in the seats will be disposed of.

(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.)