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)

Thursday, September 15, 2016

8:03 a.m. to 5:03 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

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:03 a.m.)

Call to Order

Introduction of Committees

DR. BROWN: If we could get to our seats so that we can come to order here very shortly. This is a joint meeting of the advisory committee on analgesics and anesthetic agents, and drug safety, and the pediatric advisory committee.

Let me say first good morning to everyone. I'd first like to remind everyone to please silence your cell phones, any smartphones you have, and any other devices, if you have not already done so. So, Rae, go ahead and do that.

I would also like to identify the FDA press contacts. Sitting in the back, I believe are Sarah Peddicord and Michael Felberbaum, who are now waving to us.

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

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. Let's start down on my right, and then tomorrow, we're going to start hearing people. So if we could start down here at the end.

DR. HERRING: Joe Herring. I'm the industry rep for the analgesia and anesthesia product advisory committee.

DR. MALDONADO: I'm Samuel Maldonado, industry representative for the Pediatric Advisory Committee.

DR. CRAWFORD: Good morning. My name is Stephanie Crawford. I'm professor and associate head in the Department of Pharmacy System Outcomes and Policy at the University of Illinois at Chicago. And I'm a consultant to the Drug Safety and Risk Management Advisory Committee.

DR. RUHA: You can see I'm new here. My name is Michelle Ruha. I'm from Phoenix, Arizona.

I'm a medical toxicologist, and I am representing the Drug Safety and Risk Management Advisory Committee.

DR. LASKY: I'm Tammy Lasky. I'm an epidemiologist with a special interest in pediatric medication use. I work as a consultant, and I am here as a temporary member of the Pediatric Advisory Committee.

DR. KIBBE: Art Kibbe, professor emeritus, Wilkes University in the school of pharmacy, specializing in formulation design and pharmacokinetics, and I'm a consultant to the FDA.

DR. JONES: I'm Bridgette Jones. I'm an allergy immunologist and pediatric clinical pharmacologist. I am the AAP representative on the Pediatric Advisory Committee.

DR. HAVENS: Peter Havens. I do pediatric infectious diseases at the Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee. I'm a member of the Pediatric Advisory Committee.

DR. HOEHN: Sarah Hoehn, pediatric critical

care at University of Kansas, and Pediatric Advisory Committee.

DR. CATALETTO: Mary Cataletto. I'm a pediatric pulmonologist at Winthrop University Hospital in New York, and a member of the Pediatric Advisory Committee.

DR. NEVILLE: I'm Kathleen Neville. I'm a pediatric clinical pharmacologist and hematologist/oncologist, and I'm a temporary member for this meeting.

DR. NELSON: My name is Dawn Nelson. I'm a professor of audiology at Central Michigan University. But in this capacity, I'm a patient advocate for the hematology/oncology group. My daughter has sickle cell anemia.

DR. HIGGINS: I'm Jennifer Higgins. I'm probably the only gerontologist on this panel, so I'm going to have an interesting perspective. I'm the consumer representative for AADPAC.

DR. CRAIG: David Craig. I'm a clinical pharmacy specialist at Moffitt Cancer Center. I'm on the anesthetic and analgesic drug advisory

committee.

DR. PATRICK: Stephen Patrick, a neonatologist from Vanderbilt University School of Medicine, and my research focuses on opioid use in pregnancy and outcomes for infants.

DR. MCCANN: Mary Ellen McCann. I'm a pediatric anesthesiologist at Boston Children's Hospital.

DR. WADE: Kelly Wade. I'm a neonatologist at Children's Hospital Philadelphia and University of Pennsylvania School of Medicine, member of the Pediatric Advisory Committee.

DR. HARRALSON: I'm Art Harralson, associate dean for research at Shenandoah and George Washington University in DC. And I'm a consultant.

DR. GERHARD: Tobias Gerhard. I'm a pharmacoepidemiologist at Rutgers, and a member of the Drug Safety and Risk Management Advisory Committee.

DR. KAYE: Good morning. I'm Alan Kaye. I'm professor, program director, and chairman of the Department of Anesthesia at LSU School of

Medicine in New Orleans.

DR. BROWN: I'm Rae Brown. I'm a pediatric anesthesiologist at University of Kentucky, and chair of the anesthesia and analgesia advisory committee.

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

DR. EMALA: Charles Emala. I'm an anesthesiologist and vice chair for research in the Department of Anesthesiology at Columbia University, New York.

DR. BATEMAN: Brian Bateman. I'm an anesthesiologist at the Massachusetts General Hospital.

DR. WHITE: Michael White. I'm a pediatric cardiologist at the Ochsner Health System and Ochsner Clinical School, New Orleans, and PAC member.

DR. HUDAK: Mark Hudak. I'm a neonatologist, University of Florida College of Medicine in Jacksonville, and chair of the PAC.

DR. DRAKER: Bob Draker. I'm a member of

the PAC and pediatric hematology and transfusion medicine from Syracuse, New York.

DR. CNAAN: Vita Cnaan. I'm a biostatistician at Children's National Health System and GW University in DC, and I'm a member of the Pediatric Advisory Committee.

DR. TURER: Christy Turer. I'm an internist and pediatrician at the University of Texas Southwestern Medical Center in Dallas, and a member of the Pediatric Advisory Committee.

DR. SHOBEN: I'm Abi Shoben. I'm an associate professor of biostatistics at the Ohio State University, and I'm a member of AADPAC.

DR. FLICK: Randall Flick, pediatrician, anesthesiologist, intensivist, Mayo Clinic.

DR. WALCO: Gary Walco, director of pain medicine, and professor of anesthesiology at Seattle Children's.

DR. MAXWELL: Lynn Maxwell, pediatric anesthesiologist, Children's Hospital at Philadelphia and the University of Pennsylvania, and temporary member of the Pediatric Advisory

Committee.

DR. CZAJA: Angela Czaja, a pediatric intensivist at Children's Hospital Colorado, University of Colorado, and I'm a temporary member.

DR. YAO: I'm Lynne Yao. I'm a pediatric nephrologist, and I'm the director of the Division of Pediatric and Maternal Health at FDA.

DR. FIELDS: I'm Ellen Fields. I'm the deputy director of the Division of Anesthesia, Analgesia and Addiction Products, and I'm a pediatrician as well.

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

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

DR. BROWN: If we could go back to Dr. Alexander, if you could introduce yourself, please.

DR. ALEXANDER: Hi. Good morning. I'm Sean

Alexander. I'm a pediatric anesthesiologist at Children's National Medical Center, and also the current chronic pain director at the medical center.

DR. BROWN: And Dr. Gupta on the telephone?

DR. GUPTA: Good morning. This is Dr. Gupta. I'm a chronic care and [indiscernible] professor at Drexel University College of Medicine.

DR. BROWN: And Dr. Tyler on the telephone?

DR. TYLER: This is Linda Tyler. I'm the chief pharmacy officer at the University of Utah, College of Pharmacy.

DR. BROWN: Thank you to everyone for coming this morning and not only to the members of the panel, but to the folks in the audience.

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 chairperson. We look forward to a productive meeting.

I might say that, for folks that want to ask a question or make a comment, if you would turn your little card up on its side, it will allow Stephanie and I to be able to identify you rather than missing your hand.

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 the 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.

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. Drs. Herring and Maldonado 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 the 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 has 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 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

DR. HERTZ: Good morning. Dr. Brown, members of the Anesthesia and Analgesia Drug

Product Advisory Committee, members of the Drug Safety and Risk Management Advisory Committee, and members of the Pediatric Advisory Committee, and invited guests, we thank you for joining us here today.

We appreciate your participation in this meeting where we will be discussing a number of critically important issues. Over the next two days, you're going to hear a broad spectrum of invited speakers and FDA staff as we plan to discuss the development of opioid analgesics for the management of pain in children.

The serious public health problems associated with misuse and abuse of prescription opioid analgesics, and the problems of addiction, overdose and death, are always in our mind when we discuss opioid analgesics, but especially so when we consider their evaluation and use in a population that's considered vulnerable, the pediatric population. But we also have to remember that children experience pain in a number of settings, and the imperative to relieve their pain

and suffering is no less great than for adults.

Most of the analgesic products used to manage pain in children, opioid and non-opioid, do not have pediatric-specific information about efficacy, safety, or even dosing, and that's because they haven't been studied in children. The studies that we have required for these products are intended to fill in these gaps to help the pediatric healthcare providers deliver the best possible care to their patients.

As you can see with our pretty extensive agenda for this meeting, we have asked for help from a number of experts in the field, and we have in particular also asked for assistance from the American Academy of Pediatrics to help with a variety of speakers and to help set the background for today.

So I'm going to just introduce our next speaker, Dr. Rohit Shenoi, who will present the overview of relevant issues rather than taking that on myself this morning. So, once again, thank you very much. And Dr. Shenoi?

Presentation - Rohit Shenoi

DR. SHENOI: Good morning, everybody, and thank you to the FDA for the opportunity to present the American Academy of Pediatrics viewpoints on the importance of studying drugs and labeling in pediatrics, and specifically as they relate to opioids.

I am a pediatric emergency medicine specialist who works in Texas Children's Hospital in Houston. And in my practice, I'm called to treat patients in severe pain oftentimes, those who sustain injuries from motor vehicle crashes, falls, burns, patients with sickle cell crisis, and some patients with post-op situations where they have breakthrough pain. I also treat patients with acute drug overdose.

I'm a member of the AAP committee on drugs. The AAP is a non-profit organization of about 66,000 pediatricians, pediatric medical subspecialists, and pediatric surgical specialists. The organization is dedicated to the health, safety, and wellbeing of infant, children, and

youth. It's been a longstanding AAP policy that it's not only ethical, but also imperative, that new drugs to be used in children should be studied in children under controlled circumstances.

The Best Pharmaceuticals for Children Act, BPCA, and the Pediatric Research Equity Act, PREA, have revolutionized pediatric therapeutics. More than 637 pediatric label changes have been made as a result of BPCA and PREA. BPCA and PREA were made permanent in 2012, giving children a permanent seat at the drug development table.

The timeline for BPCA and PREA start back in 1977 when the AAP issued a policy statement on the guidelines for ethical conduct of studies to evaluate drugs in pediatric populations. The pediatric incentive was enacted as part of the FDA Modernization Act, and the Pediatric Rule was published a year later. A federal district court struck down the Pediatric Rule in 2002, necessitating Congress to enact PREA.

In 2007, BPCA and PREA were re-authorized as part of the FDA Amendments Act. And as recently as

2012, BPCA and PREA were made permanent law as part of the FDA Safety and Innovation Act.

BPCA and PREA have increased our experience and understanding of pediatric clinical trial design, extrapolation, and formulations. We have learned that drugs, which were previously thought to be safe in children, do not turn out to be so. We have learned about optimal dosing in children. New indications of drugs in children have been discovered, yet 50 percent of drugs used in children are still off label, and this absence of approved labeling, FDA labeling, is a barrier to access new therapies for children.

I would like to draw your attention now to the non-medical use of prescription opioids. In 2013, there were three-quarters of a million Americans treated for the non-medical use of prescription pain relievers, and almost 19,000 opioid analgesic overdose fatalities in 2014. This was an increase of by five-fold since 1999.

Around 7000 people are treated daily in our emergency departments for incorrect opioid use, and

almost 1 in 5 ED visitors are prescribed opioids at discharge. Opioid use disorders cost us $72 billion in medical costs annually. This graph shows you the increase in the number of opioid prescriptions for the 15-year period from 1998 through 2013, and the parallel increase in the prescription opioid deaths as well.

So children should be part of the national dialogue, and that's because children represent a quarter of the U.S. population. The rate of the opioid prescriptions in adolescents aged 15 to 19 has doubled in recent years, and 2 million Americans above the age of 12 have either abused or were dependent on opioid pain killers in 2013. Among teenagers who illicitly use drugs, opioids contribute to significant morbidity and mortality.

The need for effective pediatric opioid misuse and addiction countermeasures is being addressed by the AAP. Their committee on substance abuse and prevention is working to promote the use of screening, brief intervention, and referral to treatment for adolescent substance use in a primary

care setting. They are working to develop clinical practice guidelines for the treatment of opioid use disorder specifically for adolescents. Later on in this meeting, you will hear from Dr Sharon Levy, who is the past chair of this committee, on the same topic.

The AAP also strongly supported the passage of the Protecting Our Infants Act. This act advances the federal government activities to improve treatment and identification of babies with the neonatal abstinence syndrome. It also improves the care of pregnant women using opioids.

For refractory pain conditions, pediatrics include those children in the post-operative period who have had major surgery, such as those with spinal surgery, correction of birth defects, relapsed cancer, children with sickle cell pain crisis, and those who have extensive trauma.

So our overarching goal should be that we should ensure that patients with pain receive appropriate analgesia, in appropriate dosing, for an appropriate duration of time. But we must be

equally aggressive in preventing and treating opioid use disorders, so we need a balanced policy.

As I mentioned before, the non-medical use of prescription opioids is a public health crisis. In public health, we use the Haddon's matrix to better characterize interventions that can be targeted to alleviate this problem.

They can be directed at the agent, in this case the prescription opioids, the host, and the physical environment. And in this case, the event is prescription or diversion of opioids. You can have interventions prior to the event, which is primary prevention, or those after the event, which is tertiary prevention, or post-event. Generally pre-event, primary prevention is much more cost effective because there is a better return on the investment.

So we do need better methods of using actually non-opioids in pain management and ways to disseminate this information. We need better prescription drug monitoring programs; opioid return and disposal policies and practices;

medication assisted treatment programs; and drug abuse prevention education and training. But I will be focusing on three discussion issues today, namely research and development, pediatric drug labeling, and post-marketing surveillance.

Prescription opioid research and development in children when we study these, they involve elements characteristic to all drugs, such as drug absorption, metabolism and elimination, drug efficacy and drug adverse reactions.

Then there are pediatric-specific issues, namely those that work on growth and development. The clinical trial study designs in pediatrics are different from those in adults. The evidence for long-term efficacy of opioids for chronic pain is limited.

In addition, there's a lack of publication of important data, in part because of industry sponsorship. Industry may have reluctance to publish because the pediatric exclusivity studies are typically completed later in the drug life cycle, and the economic benefits of this

exclusivity typically come from continued marketing protection of sales to adults. And once additional marketing protection is obtained, sponsors may not find the need to publish as a worthwhile investment. Efficacy studies and those with positive labeling changes are more often published, whereas studies which have negative results, which still contain important information, may not be so.

When we turn our attention to premature babies and neonates, most medications used to treat have not been studied for their safety and efficacy, and the challenges are similar, ethical issues, the concern for long-term effects on neuro development outcomes. They represent a relatively small market to the industry. And then the development of permanent injury, such as whether they're affected by the drug or not, all these have an important say in this.

So given the considerable morbidity and mortality intrinsic to premature babies and their complex physiology, we need randomized masked placebo-controlled trials with novel study designs,

such as the add-on aspects, drug superiority studies assessing the improved efficacy of one drug over the other, and then studies short-term and long-term outcomes, with surveillance continuing until school age.

Let me turn your attention to pediatric drug labeling with the OxyContin story. This is an extended-release version of oxycodone. Under BPCA, the FDA issued a pediatric written request to the manufacturer to study oxycodone and OxyContin in children, which was reviewed by the FDA pediatric review committee.

Safety and pharmacokinetic studies were performed in likely pediatric patients, which eventually led to pediatric labeling. Physicians receive specific information now to safely manage pain in a subgroup of patients, those requiring mainly a minimum daily dose of 20 milligrams of oxycodone. Unfortunately, the negative publicity due to prescription opioid misuse led to an FDA moratorium on new opioid labeling for children.

Just this week, a study was published in

JAMA Pediatrics where the contribution of oxycodone prescription, that all prescriptions of oxycodone contribute only 0.17 percent in pediatrics really, so that's a really small amount.

Pediatric labeling of opioids is rather limited actually. While we do have some information on fentanyl and oxycodone, hydrocodone, there's not much information on the safety and efficacy for morphine and methadone and hydromorphone. These medications are prescribed almost daily in our practice.

The FDA has responded to the challenge by instituting labeling changes for extended-release and immediate-release opioids. They've been most specific about the indications for the use of these medications. They've added boxed warnings on the risk of misuse. They've enhanced the safety information, such as drug interactions and the possibility of neonatal opioid withdrawal syndrome, and called for post-marketing studies for extended-release opioids.

So clinical trials may not be able to detect

all possible risk because they have a smaller number of patients and there may not be a long duration of time that these patients have been studied. So the FDA should focus on drug safety over the drug's lifetime having a specific monitoring plan considering the scientific data, patients' perspective, ethical issues, and the risk-benefit analysis.

In summary, all drugs used to treat children should have age appropriate evidence sufficient to provide information for labeling, and we should also work diligently to address the public health crisis of opioid addiction.

BPCA and PREA have been enormously successful in ensuring the study and labeling of drugs in children. We want that momentum to continue. We should advance a rational and critical study of drugs in children through conducting and/or collaborating in well designed pediatric drug studies, including national consortium studies. Journals should be encouraged to publish results of all well-designed

investigations, including studies which have negative results.

We should consider the off-label use of drugs in select circumstances, such as drug shortages. And then labeling status should not be the sole criterion that determines the availability on a formulary or reimbursement status if its prescribed for the child. I thank you for your attention.

(Applause.)

DR. BROWN: Thank you, Dr. Shenoi.

We need to go back and introduce two members of the panel that were not here when we were doing our initial introductions. Dr. Chai, if you could introduce yourself.

LCDR CHAI: Lieutenant Commander Grace Chai, deputy division director for drug utilization in Division of Epidemiology II in OSE.

DR. BROWN: And Dr. Nelson?

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

DR. BROWN: Thank you. We're now going to

proceed with the presentations from the FDA and Dr. Lynne Yao.

FDA Presentation - Lynne Yao

DR. YAO: Thank you. Thank you to the members of the committee. I want to echo Dr. Hertz's thanks to all the members of these three committees that have come together, hopefully to give us some good guidance on how to proceed with the problems and challenges that we have in understanding how to appropriately develop drugs to be used in pain, specifically opioids in children.

The goal of my talk is really to provide all of you, who are advising us today and tomorrow, on the regulatory framework and context for which drug development occurs in children. Many of you I know from my experiences with you on the pediatric advisory committee are already well versed in these regulatory considerations. But for the sake of making sure everybody is on the same page, I will take a few minutes to review these issues.

In general, we work under the principle, as practicing pediatricians, regulators, and drug

developers, that pediatric patients should have access to products that have been appropriately evaluated. And indeed, development programs should include pediatric studies when pediatric use is anticipated. This is from an international harmonization document, or guidelines, in relation to the investigation of medicinal products in children.

The problem, as has been described by Dr. Shenoi, is that because of many different situations, that metabolism in children may differ from adults, that there has always been this concern about harming children through research, or lack of incentives for drug companies to conduct clinical trials in children, has led us to, practicing pediatricians, to either one of two choices, neither of which is really necessarily the best for our patients.

The first is really just not to use a drug if it hasn't been approved, and then you might be potentially ignoring a beneficial treatment to a child who needs it. The other is to treat with

medications off label because the information is limited or is based on publication, but not based on a review of the information by FDA, and that would be off-label use.

So it was clear that the off-label use, as Dr. Shenoi had described, was the common practice before these two drug development laws were passed by Congress. First, and I'll go into a little bit of detail in each of these drug laws -- the first is the best Pharmaceuticals for Children Act, or BPCA.

What this act did was to authorize FDA to issue requests for studies from drug companies, and to do those studies voluntarily. The FDA also, under the BPCA act, or BPCA, allowed FDA to partner with NIH to do studies to support labeling of products in certain situations, generally when these products are already off patent. And then of course the Pediatric Research Equity Act, which requires companies to assess the safety and effectiveness of products in pediatric patients.

So if we compare BPCA and PREA, under PREA

and BPCA, these laws pertain to the development of drugs and biological products, but not devices. In addition, as you see the differences here that I've outlined, under PREA, studies may be required when drug developers are studying indications in adults, however under BPCA, those studies are voluntary.

Under PREA, we are not allowed or authorized to expand the indications that are being sought in adult drug development. However, under BPCA, FDA can ask for additional studies that may be of public benefit to children. As you can see that the goal of both of these is that we would like to have the information reviewed, and that information added to product labeling.

Importantly, what does not appear in either of these two pieces of legislation is a different evidentiary standard for approval. That is, for product development in children, FDA and drug developers are held to the same evidentiary standard. There is no recognition that we can go with less information in children, that it would be okay to use a different or lower standard.

Therefore, for a product to be approved in children, the product must demonstrate substantial evidence of effectiveness and clinical benefit. And how clinical benefit is defined is an impact on how a patient feels, functions, or survives. It can also be defined as a meaningful improvement or delay in progression of an aspect of a disease.

Well then how is substantial evidence defined? What do we look for in terms of evidence to support approval of a product in the United States? That evidence generally should consist of adequate and well-controlled investigations. And adequate and well-controlled study, I won't both to go into the details here, but basically the idea of the adequate and well-controlled study is so that we can distinguish the effect of the drug from other observations or effects.

I might also point out here, although not a real important component of my talk, that there is the ability to use what we already know from adult studies, that is adequate and well-controlled studies in adults, to allow for more efficient

product development through the concept of pediatric extrapolation.

Again, this is beyond the scope of this talk, but I do want to point out that just because substantial evidence is required does not mean that in all cases that an adequate and well-controlled study will be necessary. However, this is the standard, and so if we're going to use anything less or different than adequate and well-controlled study, there should be well described reasons and justification for doing so.

So moving on to these specific laws. The Pediatric Research Equity Act requires, as I said, when a drug developer is submitting or developing a drug or submit an application for a new active ingredient, a new indication, a new dosage form or dosing regimen, or route of administration, that the Pediatric Research Equity Act allows for FDA to require companies to support the safety and effectiveness of the drug in all relevant pediatric subpopulations, and that these studies should be conducted using age appropriate formulations.

It also allows for FDA, under certain situations, to either waive or defer these studies such that at the time of the adult approval, there may not be a need for any pediatric studies, in which case we would grant a waiver, or to allow for these pediatric studies to be conducted post-approval.

A waiver may be granted only under very specific circumstances, and I've outlined the four circumstances here. Number one, the studies are impossible or highly impracticable. Number two, that the drug or biologic product would be unsafe, and that information should appear in product labeling; that the product does not represent a meaningful benefit to what is existing, and that is not likely to be used in a substantial number of patients; or that reasonable attempts to produce a pediatric formulation have failed.

Deferral of pediatric assessments can be granted. And again, this means that these studies can be done post-approval if the product is already ready for use in adults. And this is again to

acknowledge that we don't want to delay the availability of a drug in adult population if it's already ready to go for the sake of doing the pediatric studies.

In terms of the issuance of deferrals and waivers, FDA has a very clear and well-worn process to assess whether or not deferrals and waivers are or can be applied. The OND review divisions and sponsors discuss these requirements early in the drug development process.

There is the requirement now for sponsor to submit a pediatric study plan, generally during the mid-stage of development at the end of phase 2. And that document should include an outline of the pediatric studies or the plans that the applicant plans to conduct, and it also should include any requests for waivers or deferrals. That study plan should also include the justifications, the rationale, and any information that supports the sponsor's plan. However, the final decision about waivers and deferrals are not made until the time of the application approval.

Unlike PREA, under the Best Pharmaceuticals for Children Act, FDA can ask the sponsors or drug developers to voluntarily conduct studies via a document called the Written Request. The idea of the written request is that FDA is able to review information about the potential health benefits of a product in the pediatric population, and in doing so would review all potential indications. The written request that FDA issues would then include all of those indications, whether they are approved or unapproved, under study for adults or not under study for adults.

A sponsor may actually request a written request be issued by submitting a proposed pediatric study request, and sponsors often will ask for these written requests to be issued, and they contain the studies and the rationale for the studies, and the plans for formulation development.

If a sponsor has been granted a written request, that is FDA has issued a written request, then the sponsor is eligible for pediatric exclusivity for the successful completion of the

written request, the studies under the written request.

As far as exclusivity, the specific terms are that if the studies are conducted appropriately, and have met all the terms of the written request, they are eligible for an additional six months of exclusivity, which attaches to all moieties or all different moieties of the product that are currently marketed and have existing exclusivity and patent.

Importantly, Congress also understood that doing these studies was important, and that the exclusivity should not simply be rewarded because the studies were positive. I might also point that under PREA and BPCA, there is a requirement to include in labeling both positive and negative studies, which is clearly a difference than in labeling for approvals within the adult population.

As part of the review process for all of submissions under BPCA and PREA, FDA has an internal Pediatric Review Committee, or PeRC, that was established to review and carry out

consistently the statutory requirements under these two laws.

The committee membership includes members with expertise in pediatrics, clinical pharmacology, and statistics. We have attorneys. We have ethicists. And we have specialists in pediatrics to review these products and these submissions. We generally meet for about three hours a week, and we reviewed almost 800 submissions last year. All of these submissions related to BPCA and PREA are then referred back, the PeRC recommendations are referred back to the divisions for their final approval.

In addition, as you may have heard, and many of you are sitting on the panel, members of the Pediatric Advisory Committee, this committee was established under BPCA and PREA. And this committee includes membership from a broad and diverse group of pediatric practitioners, stakeholders, drug developers, and advocates.

Under the requirements, under the statutory requirements, there is a mandated review of

pediatric safety 18 months after a labeling change under BPCA or PREA, and these findings generally of those reviews are presented at the Pediatric Advisory Committee. I want to point out that we've reviewed, over a five-year period, over 181 products. Yesterday's meeting reviewed 10 products and 2 vaccines, in addition to device safety.

So in summary, I wanted to describe the success of BPCA and PREA. Dr. Shenoi has gone over some of these. But the importance we believe here at FDA, and for those people who are prescribing and caring for children, is that we have now over 600 pediatric labeling changes that provide information we hope that help to safely and effectively prescribe drugs to children.

All of the requirements under BPCA and PREA are carefully scrutinized during pediatric product development by committees within and external to FDA. In fact in 2014, of the 36 products where labeling changes, pediatric labeling changes occurred, none of them were discussed by an advisory committee because the internal review was

considered to be very thorough.

In 2015, there were only two that went to advisory committee and largely because these studies included both adults and children down to 12 years of age, but not specifically because there was a pediatric issue that required discussion.

Then finally, the pediatric focused post-marketing safety reviews are an important component of ensuring the safety of products once they've reached the market and been approved for use in children. Thank you.

DR. BROWN: We're going to have clarifying questions after all of the FDA presentations. Next, Dr. Skip Nelson is going to speak for the FDA.

FDA Presentation - Robert Nelson

DR. NELSON: Good morning. I was asked to give you an overview of the additional safeguards for children in clinical investigations as you've discussed the clinical trials and how they should be approached in pediatrics.

So to set the context, we have evolved from

a view that children must be protected from research to a view that we must protect children through research. The consequence of protecting children from research is the off-label use of marketed products with insufficient knowledge of dosing, safety, and efficacy of drugs in children. And thus protecting children requires data to support the safe and effective use of drugs and biological products in pediatric patients.

Now this need for data places on us an obligation to make sure that the protocols that we're enrolling children in are both scientifically necessary and ethically sound, and children are widely considered to be vulnerable, and thus require some additional protections.

I'm going to walk through those protections, talk a little bit about extrapolation and about what I call the low-risk and high-risk pathways, and then just a couple slides on parental permission and child assent. And for those of you who have the slide deck, I'll be skipping some of the slides in the interest of time.

The basic ethical framework has four principles that can be derived from our additional safeguards. First, children should only be enrolled if the scientific and/or public health objectives cannot be met through enrolling subjects who can consent personally.

Absent a prospect of direct therapeutic benefit, the risk to which children are exposed must be low, otherwise children should not be placed at a disadvantage by being enrolled in a clinical trial, and I'll show you how that works out in the framework that's provided. And then vulnerable populations unable to consent, including children, should have a suitable proxy to consent for them.

Now, I view these as nested protections. The most important is this issue of scientific necessity. If you don't have to do the trial in children, you shouldn't do the trial in children. The second is the nest or the appropriate balance of risk and benefit. And then finally you have parental permission and child assent.

The first principle is what I call the ethical principle of scientific necessity. The practical application of this principle is extrapolation, which I'll talk about briefly, where one decides, based on the similarity of the disease and the similarity of the response to treatment, that you don't need to do an efficacy trial.

This idea that you should enroll consenting adults before children derives from the requirement for equitable selection. We often think of equitable selection to be race, ethnicity, and gender. But if you look back at the National Commission's report in 1978, they spoke about equitable selection in the context of social justice to say you should not enroll children unless it's necessary to do so.

The general justification of research risk in both adults and pediatrics are that the risks to subjects must be reasonable in relationship to the anticipated benefit to subjects, if any. What's important is this notion of if any to subjects says in adults, you can put them at risk for knowledge,

but in children we place a cap on the risk that you're allowed to place children at for knowledge alone.

These are the framework and the categories that we have. So the first is, if there's no potential for direct benefit for children, basically you must restrict the risk to which they're exposed to either minimal risk or a minor increase over minimal risk, and I'll talk about those briefly.

Otherwise, if there is risk that's greater than a minor increase over minimal risk, these risks must be balanced by the anticipated direct benefit to the child, and that risk-benefit balance must be comparable to the available alternatives. And that's where the idea of not placing a child at a disadvantage from being in research comes from.

So there are two key concepts behind this framework. The first is prospect of direct benefit, because the risks to which you may expose a child depend upon this. And so defining direct benefit is an essential aspect of the ethical

acceptability of the interventions and the research protocol.

The second is compiling an analysis. A protocol usually includes a number of different interventions, some of which may offer direct benefit, some of which do not, and you need to analyze the appropriateness of the risks of those components of the protocol separately.

So let's talk briefly about extrapolation. Generally, understood extrapolation, an inference from the known to the unknown; you don't know what's going to happen in pediatrics, but you have data to suggest that you can extrapolate, and so you extrapolate efficacy.

Now we have a specific legal definition, which is if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the FDA may conclude that you don't need to do an efficacy trial and may have adequate data to allow labeling if you have information about dosing and safety. But as I'm going to point out in the next two slides, this is

a powerful tool that can be used carefully.

This is an article that was published in 2011, which is a summary of approaches to extrapolation and shows you where we were unable to extrapolate. So there's insufficient data to say that the course of the disease and response to treatment is similar. That was 17 percent of the time.

Partial extrapolation, which can range all the way from a single trial, as Lynne pointed out, that substantial evidence of efficacy usually requires two sources of data, either two clinical trials or one clinical trial and another source of data that would be supportive. Partial extrapolation means there's only one avenue of information that could range from a clinical trial to perhaps some pharmacokinetic/pharmacodynamic data. And then full extrapolation means you can just target, if you will, the adult exposure doing PK, pharmacokinetics, and then some safety data.

The reason I say this is a powerful tool to be used carefully, it's self-evident that if you

don't have to do a clinical trial, you're going to get the label. So if you look at this fully, 90 percent of those products where PK and safety only was necessary got the label. And if you had two clinical trials, meaning no extrapolation, only 37 percent got the label. My point about this is, if we're wrong about extrapolation, and their ought to be data in support of extrapolation, then we're products on the market that don't work.

I'm going to talk now about the low-risk and the high-risk pathways. The low risk -- and this is where I say linking science and ethics. So you need data to be able to argue either that the risk of administering that product is sufficiently low, to where you don't need to think about the prospect of direct benefit, or you need data to say that what you're going to do offers a sufficient prospect of direct benefit to justify the risk. And that's the low-risk and the high-risk pathway.

So the low-risk pathway is where minimal risk and this minor increase over minimal risk come in. Minimal risk is defined as the daily-life

activities, or routine physical or psychological examinations. Now generally, the recommendation is you think about this in the context of a healthy child and not what's happening to a child who is ill. And generally, we don't consider the administration of experimental products to be minimal risk.

Now interventions that have more risk could have slightly more than minimal risk, and you could in fact enroll children with a disorder or condition, but again there's no definition of a minor increase rather than a slightly more than minimal risk. And you can only do this in children with a disorder or condition, which is not defined in our regulations.

A proposed definition by the Institute of Medicine is that this would be either a disease. In other words you have a set of characteristics or evidence to suggest the child has a disease, or is at risk for the disease. Obviously if you're doing preventive interventions, the child may not have the disease but you're trying to prevent the

disease, and that would be where the child has a disorder or condition. Many vaccine trials are done in that context. Children are at risk for measles, and so it's reasonable to enroll them in a trial of a measles vaccine.

So key points about the low-risk pathways, you need to have some data to be able to estimate the risk. If you have no data, you can't say it's low risk. Otherwise, you then have to move on to the higher risk. And I might point out that some single-dose PK studies, there may be sufficient data from adults, or perhaps even from off-label pediatric use, to say that the risk is sufficiently low to be able to do a single-dose pharmacokinetic study. But longer term dosing is generally now considered low risk.

Now the high-risk pathway, and this again is to show you the regulations around 50.52, the risk must be justified by the benefit, and then this risk-benefit balance must be comparable to the alternatives.

So what about this prospect of direct

benefit? The idea is that the child who is enrolled in the research has the opportunity to potentially benefit from the intervention that's in the protocol. It's not that the results would benefit children at large, and it's not from other clinical interventions in the protocol, which is the importance of component analysis.

So you need to ask yourself, what are the data in support of this? Does it make you reasonably comfortable? Is the dose duration appropriate? And for diagnostic procedures, one way of thinking about it is would this normally be done in clinical practice as a surrogate for whether or not there's a benefit, because presumably clinicians are making decisions about doing diagnostic studies presumably because there'd be a benefit to that information around the management of that child.

But of course the necessary level of evidence to support a prospect of direct benefit is less than efficacy, because otherwise we're in a sort of vicious loop. We need evidence of efficacy

before we can even do a trial, which makes no sense. And this is a complex judgement by both using quantitative and qualitative data, which is set within the context of the specific disease of the child and what are the alternatives available.

So if you have a life-threatening disease, the amount of data that you may want to support moving forward in a clinical trial is going to be less robust than if it's, say, a disease that is not life-threatening.

This balance is in fact similar to clinical judgment. If you go back and look at the National Commission's report in 1978, they alluded to the fact that they framed this in the context of the kind of thinking a clinician would go through at the bedside. Are the risks worth taking for the potential benefit of this particular intervention?

Now, one comment about timing, the principle of equitable selection, meaning use adults before children, doesn't mean that the adult program should be completed entirely before you move on to pediatrics. The idea here is you need sufficient

data to be able to say you have a prospect or direct benefit that would justify the risks. And you may have that data after end of phase 2, perhaps in a life-threatening disease sometime during phase 3 development in adults.

I don't want people to be left with the misimpression that this idea that you shouldn't use children and use adults means that you need the adult program to be completed before you initiate pediatric studies. And I would argue that one of the goals perhaps would be concurrent licensure to where pediatric studies are appropriately done during phase 3 adult development to where then you have pediatric labeling done at the same time as adult approval. And that off-label practice hopefully over time would disappear. Now, that's somewhat naïve. I don't expect that will happen, but that, I think, should be a goal.

Finally, parental permission and child assent, two brief comments. Parental permission is simply agreement to the participation of the child. We use permission as the language instead of

consent since I can consent for myself, but not for you. I can permit someone to do something to you, but not consent for you to have them do that. This is dealt with similarly to informed consent, and currently the only waiver is for an exception for informed consent. We don't have to get into more discussion about that particular issue now.

Child assent is simply defined as affirmative agreement to participate in research. I've given you the provisions. There need to be adequate provisions, and you need to decide if the child is capable.

Now part of the challenge here is, unless you define what assent is, you can't really define the capability. So if you link parental permission and child assent together and understand the parent's making a decision about the risk-benefit, my own view is you don't need the child to be mature enough to make that sort of risk-benefit assessment, but ought to know why are you asking me to do this and what's going to happen to me; and ought to be able to agree to enter the trial based

on that information. But it can be waived if there are circumstances that are appropriate.

I've walked you quickly through the additional safeguards for children in research, and hopefully that provides a context for your ongoing discussion. Thank you.

DR. BROWN: Thank you, Dr. Nelson.

Next Dr. Pham from FDA.

FDA Presentation - Tracy Pham

DR. PHAM: Good morning. My name is Tracy Pham. I am a drug use analyst from the Division of Epidemiology, Office of Surveillance and Epidemiology, Food and Drug Administration. I will present the pediatric utilization of opioid analgesics to provide context for today's discussion.

The outline of my presentation is as follows. I will provide the pediatric utilization patterns of opioid analgesics from U.S. outpatient retail pharmacy, followed by the data limitations and a summary of my presentation. For all analyses, we included the extended-release

long-acting, and the immediate-release opioid analgesics shown on this slide. For the rest of the presentation, I will refer to the extended-release long-acting as ER/LA, and the immediate release as IR.

Because most of the opioid analgesics were sold from the manufacturers to the retail setting in 2015, we focused our analyses on the outpatient retail dispensing of these products. The next few slides present the extent of use of opioid analgesics in children from outpatient retail setting. First, we start with the national dispense prescription data.

This figure shows the number of total prescriptions dispensed to children zero to 16 years of age for all selected opioid analgesics. The total number of opioid analgesic prescriptions dispensed to children decreased by 35 percent from 4.6 million prescriptions in 2011, to 3 million prescriptions in 2015. The majority of opioid analgesic prescriptions were dispensed to children 7 to 16 years.

This figure shows the number of prescriptions dispensed to children for IR or ER/LA opioid analgesics in 2015. The majority of prescriptions dispensed to each pediatric age group were for the IR products. The utilization trend is similar across all time periods.

Next is the national patient level data, which follows similar trends as the dispensed prescription data. This figure shows the number of children, zero to 16 years of age, who received prescriptions dispensed for opioid analgesics. Similar to trends in the dispensed prescription data, the total number of children dispensed opioid analgesic prescriptions decreased by 34 percent, from 3.7 million patients in 2011 to 2.5 million patients in 2015.

This figure shows the number of children who received prescription dispensed for IR or ER/LA opioid analgesics in 2015. Similar to trends in the dispensed prescription data, the majority of children in each age group received prescriptions dispensed for IR products.

This table provides the top dispensed opioid analgesics in children. As discussed in the previous slide, it is important to note on this slide that the majority of children received IR products compared to the ER/LA products. Among all pediatric age groups dispensed IR products, the majority of children were dispensed combination hydrocodone/acetaminophen, and combination codeine/acetaminophen.

Among all pediatric age groups dispensed ER/LA products, the majority of patients were dispensed morphine, methadone, fentanyl/transdermal, and oxycodone ER. As discussed earlier, the number of children dispensed ER/LA products are much lower than those dispensed IR products.

Due to the recent changes of OxyContin label in children ages 11 years and older, we analyzed the national annual trends of pediatric utilization of all brand and generic oxycodone ER products. Children 7 to 16 years received most of oxycodone ER dispensed prescriptions. Overall, oxycodone ER

dispensing in this age group declined over the years.

Because the recent changes of OxyContin label occurred in August 2015, we assessed additional dispensing data with a focus on the monthly utilization trends of oxycodone ER in children to assess the impact of the labeling changes on the pediatric utilization of oxycodone ER. These analyses were recently published in JAMA Pediatrics, therefore they were not included in the drug use review provided in the backgrounder.

As shown on this figure, the number of children who were dispensed oxycodone prescriptions from retail pharmacies decreased monthly over the last few years. As Dr. Shenoi mentioned earlier in his talk, children accounted for only a small proportion of all patient dispensed oxycodone ER in each month of the study period.

To understand how long children are taking opioid analgesics for, we analyzed the duration of use for the top dispensed products based on a sample of pediatric patients with prescriptions

dispensed for opioid analgesics from pharmacies in the outpatient retail setting.

The duration of use analyses included the top dispensed opioid analgesics shown on this slide. Unlike the prescription and patient data presented in previous slides, the duration of use data are obtained from a sample of patients with prescriptions dispensed for these products from outpatient retail pharmacies and do not represent national trends.

The duration of use is the sum of the treatment episodes in days, which refer to the time period that a patient has uninterrupted therapy with an opioid analgesic. The duration of a treatment episode is determined by summing day supply of all prescriptions. Of note, the day supply of a dispensed prescription is estimated by the pharmacist.

This table shows the median and mean days of therapy for the selected opioid analgesics dispensed to children zero to 16 years. In 2015, the majority of children were dispensed IR

products, which have a shorter duration of use than ER/LA products. Among children dispensed ER/LA products, the mean days of therapy were higher than the medians, suggesting that a subset of children are treated for longer durations.

To illustrate this finding, we analyzed the proportion of pediatric patients who were dispensed the selected IR or ER/LA prescriptions with the minimum and maximum days of therapy. In 2015, approximately 80 percent of children were dispensed oxycodone ER or morphine ER, and approximately 50 percent of children who were dispensed methadone or fentanyl/transdermal had a duration of therapy of less than 31 days. Among children who were dispensed the selected IR products, over 90 percent of children had a duration of therapy of less than two weeks.

Next is the data on the top prescribers specialties. Based on dispensed prescription data in 2015, pediatric specialties including pediatricians and pediatric subspecialties were the top prescriber specialty for IR, opioid analgesic

prescription dispensed to children zero to 1 years. Dentists were the top prescriber specialists for IR opioid analgesic prescriptions dispensed to children 2 to 6 years and 7 to 16 years. During the same years, pediatric specialties were the top prescriber specialty for the ER/LA opioid analgesic prescriptions dispensed to children of all ages.

Next is the diagnosis data reported by the U.S. office-based physician surveys. Of note, the diagnoses data were searched for IR and ER/LA opioid analgesics in children zero to 16 years. However, diagnoses associated with the use of ER/LA products in this population were not captured in the database, most likely due to low pediatric use of these products.

In 2015, hernia was the top diagnosis associated with the use of IR opioid analgesics in children zero to 1 year. Conditions associated with injuries and burns were the top diagnoses associated with the use of IR opioid analgesics in children 2 to 6 years and 7 to 16 years.

There are limitations to the data presented.

The outpatient retail dispensing trends may not apply to mail order specialty or non-retail settings, such as inpatient and clinic settings. Data should be interpreted as a surrogate for patient use as it is unknown if or when the medication was actually used. There's no linkage between a dispensed prescription and a diagnosis, and no medical charts are available for data validation.

The duration of use data were conducted based on a sample of patients with dispensed prescriptions for the selected opioid analgesics. Because these data were analyzed for one calendar year, the duration may be underestimated. Product switching and concurrent use were not assessed.

Finally, diagnosis mentions were obtained from the office-based physician surveys and refer to the number of times a product has been reported during a patient visit to an office-based physician. Therefore, a diagnosis mentioned may not result in a prescription being generated.

In summary, the total pediatric utilization

of opioid analgesics in the outpatient retail setting decreased over the years. Children zero to 16 years accounted for 4 percent of the total patient dispensed these products in 2015. Our analyses also showed that the outpatient pediatric use of oxycodone ER declined since 2011, and since the recent changes of OxyContin label in August 2015.

Throughout the study time, most children receive IR products, which has shorter duration of therapy than ER/LA products. Based on physician surveys for IR products, hernia was the top diagnosis reported in children zero to 1 year. Conditions associated with injuries and burns were the top diagnoses reported in children 2 to 6 years and 7 to 16 years. This concludes my presentation. Thank you for your attention.

Clarifying Questions

DR. BROWN: Thank you, Dr. Pham.

We will now proceed with clarifying questions for the FDA or Dr. Shenoi at this time. I'm going to ask again that if you want to ask a

question, if you'll just take your card, turn it over on its side so that we can identify that. And please remember to state your name for the record when you speak.

Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. I had a clarifying question for Dr. Pham. For the 27 percent non-retail, it wasn't clear to me if that was being used in hospitals for inpatients or if that was outpatient use prescribed by hospitals. So I just wanted some clarity if that 27 percent was inpatient or outpatient.

DR. PHAM: Tracy Pham, FDA. So the 27 percent of the sale distribution for the non-retail setting, that would include inpatient non-federal hospital settings and clinic settings, anything that is not mail order or a retail setting.

DR. BROWN: Dr. Walco?

DR. WALCO: Gary Walco. This is a question for Dr. Pham as well. In looking at the utilization data, the age groupings I think, from

where I sit, it would be helpful if we could get more information.

So for example, you have a grouping of patients who are 7 to 16 years old, and that's an extremely broad age range, especially given the nature of the problem we're talking about. Is there any way to break that down so that we could see, especially adolescents and older adolescents versus younger children?

DR. PHAM: We will be able to look into our database and break the 7 to 16 years further down, but we did not perform that analysis.

DR. HERTZ: Dr. Walco, what age breakdown would be -- this is Dr. Hertz. What age breakdown would be informative?

DR. WALCO: Well I think for a couple of reasons, first in terms of the nature of pain problems and chronic pain problems, those increase dramatically in adolescents.

DR. HERTZ: I'm not asking why. I'm asking specifically how would you like to see the ages if we can get additional analyses conducted. Perhaps

not for this meeting, but --

DR. WALCO: At a minimum, I would think 7 to 12 versus 13 to 16, for example, would be helpful. And if it could be more finely graded than that, that would be really helpful.

DR. BROWN: Dr. Crawford?

DR. CRAWFORD: Thank you. Also for Dr. Pham, looking at the duration of use, your slide 17, can we clarify what was meant by uninterrupted therapy with respect to, for example, a Schedule II drug that may need a new prescription with each dispensing, how is that defined as uninterrupted or interrupted therapy?

DR. PHAM: Tracy Pham. So uninterrupted, the patient will be taking it continuously, and they will fill the prescriptions on time and meet the requirement that we set in the study.

DR. CRAWFORD: And if I may be a little clearer, if it was a prescription for a Schedule II drug in a state where it could not be refilled, would it have been counted from month to month as a new prescription each time or as continuous

therapy?

DR. PHAM: It would a new prescription each time.

DR. CRAWFORD: Thank you.

DR. BROWN: Dr. Nelson?

DR. NELSON: Yes, Dawn Nelson, for Dr. Pham. Could you just clarify, you may have stated this and I missed it, when you talked about pediatric utilization for prescription data, and you also talked about I think patient level, patient-level data, did you give a reason why there was a decline in the prescriptions over the years, or is that something that we'll cover a little bit later?

DR. PHAM: Based on our data alone, we cannot conclude that the true cause for the decline in the pediatric use. But when we look at the data there, most of the pediatric patients are getting the IR products, and the top two dispensed products are the hydrocodone/acetaminophen and codeine/acetaminophen.

So over the years, FDA has had regulatory actions on hydrocodone and codeine products, so we

think that might be the drive for the decrease in use in children.

DR. STAFFA: This is Judy Staffa. I just want to add to Dr. Pham's thoughts. As she mentioned, when we're looking a prescription data, there's no reason behind that, so we can't see in our data what the reasons are. But just stepping back, there's just been an overall decline during this time period as well. And as we all know, there's been a number of different educational efforts and other efforts going on in prescribing in general, so we can imagine that that's extending as well to the pediatric population.

DR. BROWN: Dr. Kaye?

DR. KAYE: I had a question for Dr. Nelson. I've read a number of articles on pediatric suicide, and they seem to never assess pain in the articles. Is there any data linking inadequate pediatric pain management and suicide?

DR. NELSON: This is Skip Nelson. That's not really my area of expertise, so I don't -- maybe someone else around the table would

be able to answer that question.

DR. HERTZ: This is Dr. Hertz. I think that when we get into the discussion of some of the important safety considerations or risk management, maybe we could hear from members of the committees who might be able to discuss that a little bit more.

DR. TURER: Christy Turer. I have a question regarding the appropriate use of the immediate release versus extended release. Do we have data regarding those who get prescriptions and would meet the criteria for being prescribed a long-acting agent? So, you've got to meet a certain milligram per day requirement to go on those extended-release versions.

So do we know the proportion of kids who are getting immediate release on a continual basis, who in fact would benefit from the more extended release?

DR. HERTZ: This is Dr. Hertz. We are going to be looking at a variety of data as part of our analysis of the OxyContin action. OxyContin is the

first opioid, extended-release opioid, that -- well, I'll get into it. It's actually a little more complicated than that.

It's the only recent pediatric labeling that specified a minimum dose, and that was different than the adult indication. So we don't really have that information today, but it is something that we will be collecting as part of our post-marketing assessment.

I will say that, in general -- and I don't want to speak too much for our epi folks, but we've had these conversations. It's very challenging to define prior opioid use in some of these databases when we look at this question in a number of different settings, even in adults. But it is part of the questions that we have put into the post-marketing requirements for the most recent action.

DR. BROWN: Dr. Czaja?

DR. CZAJA: I was just going to add on to that, to collaborate what Dr. Hertz said. Based on some of the data we may use, such as claims data,

it is difficult to get the exact dose that was administered to the patient or dispensed.

The dispensed information to the level of claims data usually has like the strength that was dispensed, and possibly a signal, which could include PRN when you're talking about IRs. So it does get very complicated, but we have issued PMRs to look further into that.

DR. BROWN: Dr. Czaja?

DR. CZAJA: This is Angela Czaja. I was wondering, for the impact on the pediatric labeling, if you considered using time series analysis. Just because looking at the trends before as opposed to the after, rather than using the mean monthly, just in case there was a decreasing trend but actually post-labeling change, there was actually no change.

Sorry, that was for Dr. Pham.

DR. STAFFA: This is Judy Staffa. I can take that. What we did was we just wanted to take a quick look to see what was happening, to detect whether there was any kind of a quick increase or

change in patterns. But again, the sponsor has been required to do a number of studies that will be looking at all different aspects of the impact of this labeling change.

DR. BROWN: Dr. Neville?

DR. NEVILLE: I think this question is for Dr. Pham. So on the duration of use data, and you might have said this so I apologize if I missed it, was it captured how many patients were repeat prescriptions? So we have the main duration of the IR prescriptions, but do we know how many patients got a given number of prescriptions per month or year?

So my question is, you might go on for 6 days and come off and go back on, and how or did we capture those data?

DR. MOHAMOUD: This is Mohamed Mohamoud from FDA. I work with Dr. Pham on the duration of use analysis. No, we do not have the number. This analysis was done sort of in a crude way, so we don't have the exact number of prescriptions that were given for -- we just have the mean duration

overall.

DR. NEVILLE: Is that something that ever can be captured or not possible?

DR. MOHAMOUD: I think it's possible, yes.

DR. BROWN: Dr. McCann?

DR. MCCANN: Dr. McCann from Children's Hospital in Boston. I have a question for Dr. Shenoi. And I'm sort of actually stuck on the title of his presentation where he said towards a safer and pain free tomorrow. Is that possible? And should that be our goal or should our goal be optimizing management in children who have pain?

DR. SHENOI: Yes, it is. That's what our goal should be. And it is a difficult goal, yes, but we need better ways in which we can identify pain in children and move towards that goal. So it may be a perplexing title, but I think that's the goal which we have.

DR. BROWN: Dr. Flick?

DR. FLICK: Randall Flick. Dr. Pham, could you help by giving us a little more information on prescribers? Describing prescribers in pediatrics

is not very illuminating. I wonder if there's any breakdown of the specialties of pediatrics so we can get a little better sense of who is prescribing, especially the extended-release formulations.

DR. PHAM: Tracy Pham, FDA. The pediatricians, I can provide the number, the percentage. So the general for the zero to 1 year old, for the extended release, the general pediatricians accounted for about 42 percent of the 1,909 prescriptions that were dispensed in 2015. And we also have other pediatric subspecialty, which include like surgeon, pediatric anesthesiologists, et cetera.

Then for the 2 to 6 years, for the extended release, the general pediatricians accounted for about 14 percent of the 1,480 prescriptions that were dispensed to the 2 to 6 years for the extended release. And we also see the same pediatric subspecialty for that age group.

Then the 7 to 16 years, general pediatrics accounted about for the same 14 percent of the

11,806 prescriptions that were dispensed for the extended release in the 7 to 16 years. And the breakdown of the subspecialties include very similar for the zero to 1, and 2 to 6 years.

Does that answer your question?

DR. FLICK: Sort of, but if that's all you got, that's all you got. Any sense of the indication by age? Who are these zero to 1 year olds who are getting extended release? I presume they're neonates getting methadone or something. But it would be interesting to know what the indication by age would be, especially again for the extended-release formulations.

DR. PHAM: So in our database, I think because the pediatric use of the ER/LA products is so low, that it does not capture for our diagnosis data. The diagnosis data are based on the office physician surveys, which bases off on the 3200 physician panel at an office base. And the data is collected on patient activity on one day of the month, so it's a very low sample, so we're looking at low usage. It might not be captured in the

data.

DR. FLICK: All of these data are outpatient data, correct? They're not inpatient data?

DR. PHAM: That is correct.

LCDR CHAI: May I help corroborate the answer? This is Lieutenant Commander Grace Chai. So as Tracy -- I just wanted to reemphasize that indication is not necessary to be written on a prescription when they are dispensed from like a CVS and those types of settings. However, in the backgrounder, the addendum, there's more detailed information on exactly which ER/LA opioids are dispensed in terms of the top products to the zero to 1 population. And we can see exactly what those are, and it is methadone as the top dispensed molecule.

Because the numbers are so low, as Tracy reiterated, are office-based, so this does not include inpatient physicians, didn't capture a physician reporting this on a survey. So it's very difficult to say, but at least you know which molecule they dispense as a drug. Thank you.

DR. BROWN: Thank you for that information.

Dr. Staffa, the information that we were just given about those data in the zero to 1 population is interesting, and I wonder if those data could be corroborated. I can see that methadone administered to children in a neonatal setting would be something that we would expect, but children zero to 1 in an office-based setting would be I think a little bit unexpected.

Is there some way that we can corroborate that data or expand on it, or get a better handle on it?

LCDR CHAI: We don't have the level of granularity as to who initiated the prescription, but these could include patients that are discharged from NICUs and inpatient settings, and may have continued therapy. But the physicians that usually prescribe in the outpatient setting, the office-based physician survey database that we assessed, didn't capture any of those types of prescribing.

DR. HERTZ: Right. So remember that this

would capture -- oh, sorry, this is Sharon Hertz. This would capture not just methadone prescribed for analgesia, but also to treat neonatal opioid withdrawal syndrome. So I don't think we should assume that it's management of pain in the zero to 1 on an outpatient basis.

I think there are clinical settings where practice does permit the continued management for -- I see perhaps somebody with much better knowledge in terms of first hand shaking their head on the committee. So perhaps as we discuss some of these issues with regard to the questions, the approach to different patients, this can come out more.

But it's clear that the idea of an extended-release opioid in a zero to 1 age range could be very perplexing, but I think if we consider that when it's methadone, and because of the intersect with treating neonatal opioid withdrawal syndrome, that there may be other possibilities.

DR. STAFFA: This is Judy Staffa. I just

want to address your question about data validity. As our drug utilization analysts look at these data and pull them from IMS Health and the other vendors, whenever they see anything that doesn't make sense to them or strikes them as odd, they go back to the vendor, and we do the best we can to verify that the data are correct, that they are not based on data errors, but we can only do that within a certain framework.

So I can tell you that the data, as far as the vendor is concerned, is correct as they can make it, but we can't go back actually to the pharmacies and talk to the pharmacists and ask them and check their actual prescriptions.

DR. BROWN: Dr. Patrick, do you have any comments about the administration of methadone in outpatient setting to children

DR. PATRICK: Stephen Patrick from Vanderbilt. Yes, it's not an uncommon practice to discharge infants home on methadone for neonatal abstinence syndrome or neonatal opioid withdrawal syndrome. There aren't a lot of data to

really -- there still remain a paucity of data on outcomes with outpatient management, but it is a practice that does occur in many communities.

DR. BROWN: Dr. Jones?

DR. JONES: Yes, I had a question about the duration of use data for the outpatient non-retail pharmacy data from Symphony Health. Does that data include children's hospitals as well, children hospital outpatient pharmacies?

DR. MOHAMOUD: The data includes outpatient facilities generally speaking, but specifically outpatients settings affiliated with the children's hospitals is something we can't specifically comment just because the data when we get it back, we're getting it de-identified, so it's tough for us to tell you whether these facilities are included or not.

DR. JONES: I just asked that question just because the database that we get data from for the PAC, I don't know if it's the same database or not, but it doesn't include data from children's hospitals.

DR. MOHAMOUD: So I think the database that you're referring to that's typically used with PAC reviews includes hospitals specifically, and that database specifically doesn't include children's hospitals. But this database is a little bit different, but nonetheless, it doesn't include children's hospitals.

DR. JONES: It does or it does not include?

DR. MOHAMOUD: It does not, sorry.

DR. JONES: It does not?

DR. MOHAMOUD: Does not. Yes.

DR. BROWN: Are we ever going to see those data? It would seem like that would be a large untapped group that we could define, or better understand administration of these drugs.

DR. HERTZ: We're trying to follow these data sources. This is Sharon Hertz, back here. So what specific data is the question asking about? So we can go back and try and sort out what you might have gotten in the context of PAC.

DR. JONES: The Symphony Health Solutions, I'm not sure which database is used for the PAC

data that we generally use.

DR. HERTZ: But what is the data that you're asking about to describe --

DR. JONES: Here, the duration of use data.

DR. HERTZ: You're asking -- I'm trying to --

DR. JONES: About the outpatient.

DR. HERTZ: You're asking specifically for children's hospital outpatient pharmacy data?

DR. JONES: No, I'm just wanting to know is that included in this data analysis.

DR. HERTZ: Right, so that's one question that I heard, and we'll see if we can clarify that any further. But is there any other type of setting that you have a question about, whether that's been included?

DR. JONES: No. I just wanted to know, does this include outpatient pharmacies from children's hospitals. Because I think that if it's not, then there's probably data that's maybe missing, and we're not really getting a clear picture of how the medicines are being used in a large segment of

children.

DR. HERTZ: Okay. So we're going to see if we can sort out what the PAC is using because this is the same group that will generally provide their information, our Office of Surveillance and Epidemiology drug utilization group. So we'll look into that and see if we can provide some clarity.

DR. JONES: Okay, thank you.

DR. BROWN: Dr. Chai?

LCDR CHAI: I can answer that question. What you're referring to are primarily the inpatient utilization data. So the complication is that the data sources in the U.S. are disparate, they're not very easy to collect longitudinally. So when we're looking at one patient in an inpatient setting, what may be captured when they are inpatient in terms of all the drugs that they receive and are administered, doesn't mean I could capture it, for example, in their insurance, final insurance claim, which could be a summary of all their care.

That doesn't directly link with the

outpatient retail dispensing data that we have access to, which is a nationally estimated aggregated de-identified number. And what you're specifically asking about are the clinics or pharmacies attached to children's hospitals. Because of the de-identified nature of the sources that directly contribute to our data sources, we don't have an exact answer as to what number that is, and I don't think the -- we'd have to find out, but I'm not sure if the data vendors would be able to give that to us due to the nature of their contracts as well.

But we currently do not have access to children's hospitals, but we did issue a request for information through the government contracting processes last year to look further into this because we know this is an area that we are interested in. So we're still working through the process, but we don't currently have a contract to get that data.

DR. YAO: Lynne Yao. I do want to point out -- and I think that Dr. Jones, your point is

well taken about the potential hole of not having children's hospital outpatient pharmacies included in the data.

If you go to the background amendment, background document amendment, that was submitted, there is interestingly in the zero to 1, in terms of who is prescribing, a little bit more granularity there. And I see even in the zero to 1 for the IRs, hospitalists, they're included as prescribers, or neonatal, perinatal medicine physicians prescribing the ER/LA formulations.

So there does appear to be capturing some percentage of in -- that these were prescribed in some form to a retail pharmacy, but from a hospital setting.

DR. BROWN: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. I had another question for Dr. Pham related to slides 21 and 23. It seems like there's an incongruence where 19 and 29 percent of the prescriptions from 2 to 16 are prescribed by dentists. Yet, the indication for the primary ones from ages 2 to 16 are injuries and

burns. So I know you have some limited, in terms of diagnostic data, but it didn't make sense to me that the dentists are the number one prescribers for 10 years of kids, and that didn't seem to match up with the diagnoses.

DR. PHAM: So for the office-based physician surveys data, that does not cover the dentists on the panel where the data is collected from, yes. And for the prescriber specialty, the data is based on the dispensing prescription from the outpatient retail pharmacy, and there's no linkage between dispensed prescription and a diagnosis. So that's why we see a difference in the data.

DR. STAFFA: This is Judy Staffa. Just to follow up, these are two different data sources. So you're absolutely right, when you look at the prescriber specialty, that's coming off dispensed prescriptions at the pharmacy. So the dentists, people bring prescriptions to pharmacies from dentists all the time. But when we go to the office-based survey, which is where we get indication, there are no dentists in that sample.

That's the reason for the disconnect.

DR. HOEHN: Well the disconnect makes sense. I still don't know if anyone has any input on what would be the diagnoses that makes the dentists the number one prescribers. It just seems a lot of toothaches.

DR. STAFFA: This is Judy Staffa. Actually, Dr. Bateman I think did a study earlier this year, publishing a study looking at health insurer data at tooth extractions. I don't know if you wanted to comment on that.

DR. BATEMAN: Sure. It was a research letter that we published in JAMA looking at prescriptions of opioids after surgical extraction of the teeth and reported that a very high prevalence of prescribing after that procedure, including in children. So, yes, I am not surprised.

DR. BROWN: Dr. Yao?

DR. YAO: Yes, I just wanted to also provide maybe a little bit of additional context. So even though the dentists may be the top prescribers in

the slide at 19 percent and 29 percent, that's still a large minority. In other words, if you look at the universe of the other prescribers, I think that's another area that would be helpful to review, because even though it's the top, it's still not the majority.

DR. BROWN: Dr. Neville?

DR. NEVILLE: So my question goes back to the lack of data on indication and subspecialty. Are those data being collected as part of that OxyContin post-marketing so that we have more granularity of indication in subspecialty?

DR. STAFFA: This is Judy Staffa. Yes, I believe they are part of that as well.

DR. BROWN: Which leads me to ask Dr. Yao, since we have been talking about BPCA and PREA, about the issue of post-marketing surveillance that is indicated within those two pieces of regulation.

Has the PAC been successful -- we're talking about a very special class of drugs. Has the PAC been successful in getting post-marketing information from our friends in the pharmaceutical

industry about issues concerning normal products that are not opioids? And can we expect that that will be something that we will be able to expect from them for opioid compounds?

DR. YAO: So I'll answer that question, and then I'll also allow my colleagues at FDA to add their comments. So I want to clarify a couple of things. So under BPCA and PREA, as I had mentioned, when there is the requirement or the opportunity to do pediatric studies that lead to an eventual labeling change, that triggers the requirement to collect post-marketing safety data that is then reviewed by the Pediatric Advisory Committee. So that's one piece.

On any given approval, for any drug, whether it's for adults or children, there is the ability for FDA to require additional studies post-marketing if there is a known or suspected safety concern.

So in the situation of OxyContin approval in children, we recognize that there could be some safety concerns related to the use in that

population, and therefore these post-marketing requirement studies were invoked and will be required to be reviewed.

There will be two separate but aligned processes in place to review the safety. The first is, is that under those safety post-marketing requirements, we call them FDAAA or safety PMRs, we have a whole group of specialists in the division who will be reviewing the data that come out from there. In addition to that, those data will also be used as part of the required Pediatric Advisory Committee safety review.

So I think there's a lot of people going to be reviewing the data that we've asked the -- required the sponsor actually to collect. And I'll have Judy or others add comments.

DR. HERTZ: So to add to that -- I'm sorry, this is Sharon Hertz. So in the context of the existing PMRs for OxyContin, we have asked for data that we don't know currently how to get. We don't have to limit a PMR to existing sources of data. We can ask for answers to questions that may

require developing new sources or new ways of linking data depending on the question.

So you've identified some of the challenges that we have when we're looking at a variety of our existing data sources, but the PMRs for what we've put in place most recently actually go beyond what we think is readily available. And we've done that in a number of settings, but this is a particular one that we were aware that what we were asking for was not readily available.

DR. BROWN: But under BPCA and PREA, as opposed to our experience in using opioids in adults, there's a requirement.

DR. HERTZ: The additional PMRs that we required with the approval of the pediatric language for OxyContin was not under BPCA or PREA directly, it was under our other authorities to require additional studies for evaluating safety post-marketing.

That opportunity we have for any product, and we have a number of post-marketing requirements, PMRs, for the extended-release and

long-acting opioids in general. We have them for the abuse-deterrent opioids that are separate. So we have many situations with the opioids where we are requiring additional PMRs in both adult and now in this particular pediatric setting, and that is independent of BPCA and PREA.

BPCA and PREA give us the opportunity to get the basic information we need to understand how to try and use these products safely. But if upon an approval, we think we want to follow safety or have additional safety questions, we can invoke our other authorities to put in place these type of additional requirements.

DR. BROWN: Thank you, Dr. Hertz.

Dr. Higgins?

DR. HIGGINS: With respect to the totality of pediatric studies that are conducted, what proportion are voluntary versus required under PREA or BPCA?

DR. YAO: Lynne Yao. I think I can at least partially answer that. So if you look at the early days, BPCA was, or the first incentive provisions

were passed in 1997, so most of the drug development occurred voluntarily. PREA, or the Pediatric Rule was struck down, so there was a period of time where we were kind of not sure what to do. But then in 2003, once PREA was passed, that was then the requirement, the requirement portion became available to use.

So if you look at the balance now, there is a large majority of the studies that are being conducted in children are conducted under PREA. So as an example, we have about 700 studies -- this is approximate so I don't want to give you exact numbers, but I can get that information and pass it on to you later today -- studies that have been required of sponsors as post-marketing requirement studies since 2007.

During that same period, there have been about 10 to 15 written requests issued per year. Now that may include more than one study, so you would still say in the order of 100 to 200 studies. So you can see the balance is tipped very much towards studies being done for children under PREA.

DR. BROWN: Dr. Walco?

DR. WALCO: This question may border, if not cross the line of esoteric. But as Dr. Flick raised the issues about extended-release preparations in neonates, I was struck looking at some of the material provided to note that transdermal fentanyl patches are used 17 percent of the time in infants.

So I'm looking across the room at you, Dr. Patrick. Does anybody have any clue why people would be doing that?

DR. PATRICK: The short answer is, no. I wonder about complex conditions. Pediatric palliative care might be one to discuss. But I don't know if Dr. Hudak may have a comment, but it's not common in my practice.

DR. HUDAK: This is Dr. Hudak. Yes, I think that the use of these patches is done mostly on inpatients with chronic conditions, like Stephen says. Typically, children who are being managed for hospital-acquired opioid dependency, so patients on ECMO for a long time or on fentanyl or

morphine infusions for two weeks require treatment for withdrawal. And I think this is one of the modalities that's used to try to manage that condition.

DR. BROWN: Dr. Hudak, did you have another question for the group?

DR. HUDAK: Oh, I'm sorry. No.

DR. BROWN: Dr. Chai?

LCDR CHAI: Grace Chai. Just one more note to the fentanyl/transdermal. One of the limitations that we have with the data resources that we have are the lack of the ability to do chart validation, so this is our inability to verify patient's date of births as well as if the patient is actually a child that is getting this drug.

So as prescriptions are being dispensed from pharmacies, we don't have the ability to know if perhaps by mistake they wrote the current date on the date of birth space. So it's very difficult to disentangle that, and the numbers are extremely low.

So I can't say for sure whether there is use or isn't use with these small numbers, but I do want to say that we cannot clean the data to go back to actual patient charts.

DR. BROWN: Dr. Czaja?

DR. CZAJA: Angela Czaja. I had two questions. One was for the longitudinal database. Do you have a sense of how long a particular individual is tracked across the longitudinal database? How long do they stay within that database?

And then the second question had to do with, since we're talking about access, do you have the ability to link it to parents or other adults who are receiving prescriptions for opioids within that same family?

LCDR CHAI: This is Grace Chai again. I can try to answer that question. We did not do an analysis to try to link it to the parent. I think that may be difficult to do, but I would have to check on that. As well as what the study was done was a crude analysis over one calendar year.

So of course patients may drop in and out of insurance plans, but what we try to do is actually look at it from a pharmacy level. So this could be like a prescription with like identify information that's de-identified on the vendor side, which could include name, date of birth, zip code, gender, that kind of de-identified information in order to link it. So it may include a few -- it doesn't have to be directly linked to, for example, a closed insurance plan.

I don't know if this helps answer your question.

DR. STAFFA: This is Judy Staffa. I would add to that. This is a data system where you're pulling data out of the outpatient pharmacy. So in as much as people frequent the same pharmacy, we'll see the same patients. We typically try to look at activity at the beginning and the end of the study period, but people don't enroll in pharmacies, and so it's not like insurance data, so there is some opportunity for attrition there.

To our ability, there's no ability to be

able to link to other family members using those data. Whether the data vendor can do that with the information they have, we don't know.

DR. BROWN: Dr. Flick?

DR. FLICK: Randall Flick. There seems to be kind of a pattern to the questions, and they all seem to end with, we don't really have good data. And so as we progress toward the questions, that would seem to be a theme that we're going to follow.

Sharon, you made a comment that we're asking for information from sponsors that they can't provide. As a kind of a core area, a follow-up to the lack of data, whose responsibility is it to provide those data to the agency? Is it the sponsor's responsibility? Is it the agency's responsibility to develop the data sources? Given the problem here is data, where is it going to come from?

DR. HERTZ: This is Sharon Hertz. If we think that there are questions that need to be answered regarding the post-marketing safety, we

describe those questions in our requirements. The responsibility is on the sponsor to then develop a way to fulfill the post-marketing requirement. And if that requires a new data source or some other type of research or investigation, that's their responsibility.

DR. FLICK: It seems to me that this is a bit of a piecemeal approach because rather than having a robust data source that both the agency and the sponsor can go to, to answer the endless number of questions that come up in this setting or other settings, it would seem that it would be a great leap forward for the study of pediatric drug use, appropriate and inappropriate, if we had a reasonable data source to go to.

DR. STAFFA: This is Judy Staffa. I absolutely agree with you 100 percent. And as Dr. Chai mentioned, we have put out requests for information to try to understand. Part of it is the lack of the data comes from the way health care is provided. We have a fragmented system that there are a lot of stovepipes.

So there are a lot of good data out there, but from an FDA perspective, if we're trying to understand national patterns of pediatric drug utilization, that's a challenge, because in order for these companies to provide that information, they have to have both a sample that they can look at, and then a universe to which they can project. And identifying that universe has been challenging, so we have done a lot in this space.

We have accessed data in the past and found that we weren't really clear whether what we were looking at were actually national patterns or simply local or regional patterns. And I'm sure if I look around at the practitioners at the table, practice patterns can differ across the country. So it's a real challenge. There's a real gap here.

What we're trying to do is both work on it ourselves, as much as we can, by getting the need out there and talking to people in the space. And at the same time, making requirements to get these data because we know by asking for them, we may be pushing the powers in society to actually recognize

the need and begin to collect them and put them together.

DR. BROWN: Dr. Gupta?

DR. GUPTA: I have a question on whether [indiscernible].

DR. HERTZ: The question, I believe was -- we had a little trouble hearing. The question was, I believe, is there information available on the use of the TIRF products within the pediatric age groups?

LCDR CHAI: If I understand the question correctly, it is --

DR. BROWN: Dr. Chai --

DR. HERTZ: Dr. Gupta, perhaps you can mute your phone when you're not actually speaking because we have an echo in the room.

LCDR CHAI: It is included in the tables for the prescriptions and patients data. They are in very low numbers. It's in the line that's delineated, transmucosal immediate-release fentanyl. So the TIRF products, if that was the question.

DR. BROWN: Thank you. We're going to take a 15 minute break now. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:20.

(Whereupon, at 10:06 a.m., a recess was taken.)

DR. BROWN: If we could get back to our seats now so that we can continue with the FDA presentation.

DR. BEGANSKY: We're going to go ahead and get started. I'm going to repeat the question that Dr. Gupta had asked on the telephone line since it was a little unclear, and then we're going to have Grace repeat the answer for us that she had given earlier.

The question that Dr. Gupta asked is, is there any data on the amount of use of transmucosal fentanyl in pediatrics based upon the limited data that exists?

LCDR CHAI: This is Dr. Grace Chai. It is

in the data under nationally estimated number of patients who receive prescriptions, as well as the dispensed prescription table in the appendix. And the line listing would be transmucosal immediate-release fentanyl products, with the TIRF. So the numbers are there. Thank you.

DR. BROWN: Thank you, Dr. Chai.

Dr. Galati will now continue with the presentations from the FDA.

FDA Presentation - Steven Galati

DR. GALATI: Good morning. I'm Steven Galati, a medical reviewer in the Division of Anesthesia, Analgesia, and Addiction Products, and my talk today is a broad overview of the current approach to studying opioid analgesics in pediatric patients.

As you've heard earlier in Dr. Nelson's presentation, it is critically important to study drugs in children. The spirit of this quote describes the ethical responsibility to obtain useful data in the pediatric population.

"Children are not simply small adults, but

represent a distinct patient population with potentially different needs, dosing, metabolism, and treatment requirements."

This is an overview of my presentation, and in this presentation, I'll discuss the existing opioids that contain pediatric language in their product labeling; the completed and outstanding written requests, as well as PREA post-marketing requirements; how the FDA came to the current advice we give to sponsors on study requirements of opioids in children; and what is included in this current approach.

There are currently several opioids with pediatric-specific language in their product labeling, as you can see at the top of this slide, in this list at the top of the slide. And as discussed earlier by Dr. Pham in her presentation on opioid drug utilization, the vast majority of opioid usage has been in the immediate-release opioid products. However, several of the more commonly prescribed opioids have no specific drug language in their product labeling.

The purpose of this slide is to display a list of opioid products with pending PREA requirements. And as you can see, there are a number of molecules that we have requirements for.

Written requests are an avenue which allows sponsors to voluntarily respond to requests from the FDA for additional pediatric studies. These studies are designed to determine if the drug could have meaningful benefits to the pediatric population. Here are a current list of open and completed written requests for opioid analgesics.

A key example of a recent written request is OxyContin. This was originally approved in an extended-release formulation back in 1995, and the current abuse-deterrent formulation was approved in 2010. The original written request was issued to the sponsor in 1999 with several subsequent amendments.

The applicant submitted an efficacy supplement in response to the written request in 2014, and it was subsequently approved by the FDA in August of 2015, and this included specific

language with regard to pediatrics added to the product labeling. And the language included in the product labeling is at the bottom of this slide.

Now this approval of pediatric-specific information for OxyContin had raised concern among a number of stakeholders about the impact this labeling change may have on prescriptions and usage in children. The purpose of requesting additional studies are not intended to increase usage or prescriptions in children, but rather provide additional data on the appropriate dosing and safe use in children who are already receiving treatment with opioid analgesics on an off-label basis.

As discussed earlier with Dr. Pham, FDA had conducted a review of OxyContin usage occurring off-label, and determined that based on the existing use in children, there was a public health need to provide prescribers with pediatric-specific data.

Additional safety information was identified in the completed pediatric study submitted by the sponsor in addition to published literature, which

expanded our knowledge of opioid safety. From our evolving thought processes and increased knowledge, we created novel post-marketing requirements to continue to evaluate the safety of OxyContin in the pediatric populations. And these studies 1 and studies 2 are the post-marketing requirements for OxyContin, and this was discussed earlier in the question and answer discussion. The goal of these studies is to better understand the risks associated with opioids in children.

For years, FDA required efficacy, safety, and pharmacokinetics in all populations, in all age groups. However, relatively few studies were conducted, and a small number were completed, due to challenges in designing and enrolling patients in pediatric studies. Therefore, FDA wanted to find alternative methods to obtain pediatric data to provide useful information for prescribers. An example of this is extrapolation of efficacy from adult studies.

As discussed earlier by Dr. Nelson, extrapolation is an application that expands

efficacy from adults to the pediatric population, as described in the regulation you see here. The essence of this regulation details that if both the disease and drug product are believed to be similar and act similarly in adults and children, then effectiveness may be extrapolated from completed adult studies, and this application would be relevant in pediatric pain.

If appropriately used, extrapolation of efficacy is a very useful tool that allows pediatric data to be collected more efficiently. This can maximize the relevant available information that may be used to benefit the pediatric population. And this is important because children are a vulnerable population, therefore maximizing the information obtained from the available data is of key importance.

This also allows a smaller number of pediatric patients to meet the required design standards of a study, thus allowing a more efficient pathway to draw conclusions that may inform prescribers.

Despite its usefulness, there are a number of limitations to extrapolation. And as described by Dr. Nelson, this concept only applies when we can use known facts and draw inferences, predictions, or conclusions about an unknown.

Therefore, if a mechanism of a drug is novel, we will have limited understanding of how it may act in children. Also, if the pharmacokinetic exposures are inconsistent between adults and children, it is unclear whether extrapolation of efficacy from adults is appropriate based on the pharmacokinetic data alone.

Although the primary objective in pharmacokinetic studies is pharmacokinetics, the FDA recommends sponsors still continue to collect pain scores and rescue usage in these studies to provide some context in case there are inconsistent exposures.

In December 2009, the FDA convened a workshop with experts in the field of pediatrics. This was a scientific workshop, which discussed the relevant approaches of studying acute and chronic

pain in the pediatric population. The available science was also discussed about supporting extrapolation for all analgesic drugs.

The workshop was later translated into a publication by its participants, as referenced at the bottom of this slide. And after this workshop was completed, the FDA determined how to best apply the latest science and concepts to the regulatory approach for studying analgesics in children.

Populations for studying opioids in pediatrics are reflected in the language we use and the respective indications, as you can see in this slide. As you can see, the populations enrolled differ depending on the nature of the formulation. The immediate-release formulation is used as a treatment for acute pain, and the extended-release formulation for chronic pain populations.

Enrollment is a major challenge in pediatric studies. The typical placebo-controlled design used in adults poses ethical concerns in children. Also parents are reluctant to enroll their child in an experimental drug trial, as well as the concern

about extensive blood sampling. There is also the practicality of enrolling a sufficient number of patients in the pediatric population, especially the very young age groups, such as neonates, and in chronic pain conditions where disorders are much less prevalent.

Based on our current understanding of the available science, for example the drug metabolism differences amongst different age cohorts, we extrapolate efficacy from adults down to the age of 2. And based on our knowledge of pain conditions, the study requirements differ between the immediate and extended-release opioid products.

So for example, the immediate-release opioid products, due to extrapolation of efficacy, only safety and pharmacokinetic studies are required in the 2 to less than 17-year age group. And you can see everything, including efficacy, was required in the younger age group of zero to less than 2 years of age.

This will differ from the extended-release opioid analgesic products where we allow

extrapolation down to the age of 7, but that's because we waive studies under the age of 7 due to the impracticality of studying such a low prevalence of subjects with chronic pain disorders in that age group.

Once again, design elements of pediatric studies differ between acute and chronic pain populations. For acute pain, the patient must require an opioid level of treatment, but be in an acute setting, such as post-surgery. The primary measure of efficacy in these studies would be the difference in cumulative amounts of rescue between the study drug and the placebo group.

In simpler terms, this is the difference in the standard of care required between the two groups. So for example, the standard of care may be an immediate-release opioid that a child would normally receive in the clinical setting studied, and now this solves some of the ethical and practical issues we have in pediatric studies.

For chronic pain studies, the patients require around-the-clock opioids and meet minimum

pain requirements for entry. As previously described, we extrapolate efficacy down to age 7, and waive studies in the age group under 7 years of age due to the impracticality of studying chronic pain in that population.

The population studied includes a pain population that would be expected to have prolonged pain, for example weeks to months. And some examples of these types of populations is listed in this slide under the second bullet under chronic pain.

Although efficacy is extrapolated, once again, we still recommend that sponsors collect pain scores and rescue usage in these studies that provide a context for the relative exposures between adults and pediatric pharmacokinetic data.

In conclusion, the FDA has been working for years to develop a novel approach for assisting sponsors in the use of opioids for pain in a pediatric population. This approach has evolved by the use of available science. FDA encourages sponsors to collect data efficiently to enhance the

safe treatment of pain in the pediatric population. Thank you.

DR. BROWN: Thank you, Dr. Galati.

Our next presentation will be Dr. Nallani from the Division of Clinical Pharmacology.

FDA Presentation - Srikanth Nallani

DR. NALLANI: Good morning. I am Srihanth Nallani from the Office of Clinical Pharmacology supporting the Division of Anesthesia, Analgesia, and Addiction Products. Today I'll talk about the clinical pharmacology considerations for conducting pediatric studies.

As Dr. Galati already talked about, the pediatric study planning and efficacy extrapolation, as it relates to the FDA opinion, and he also talked about the FDA workshop held in 2009 and the publication that resulted from that expert opinion workshop, that formed kind of the basis for the clinical pharmacology considerations described -- the approach taken from the draft guidance on pediatric studies for drugs and biologic products.

The PK-only approach in pediatric patients is applicable where full extrapolation of efficacy is applied. This relates to both immediate-release opioid and extended-release long-acting opioid products. Because of the limited clinical experience, and because we cannot extrapolate efficacy in the age group, approach to clinical PK in pediatric patients is described from a conduct of a PK study point of view for pediatric patients under 2 years of age.

Just briefly reiterating some points Dr. Galati mentioned and the scientific opinion expressed by Dr. Berde and coauthors in the 2012 publication, analgesic clinical trials in pediatrics are challenging and require a delicate balance between scientific, ethical, and practical concerns. The scientific opinion was that biological, empirical, and experiential basis exist to justify extrapolation of efficacy from adults to children aged 2 years for new opioids. The experts also recommend safety data may be collected, both during performance of PK and dose ranging studies.

Despite the availability of opioid drug products in various forms, there is significant variability in the clinical practice, and there is lack of unanimous recommendation across the pain societies or hospital systems regarding different conditions of pain. Therefore, the clinical pharmacology approach is to assume, as recommended by the draft guidance, indicated in lines 377 through 384, that there is no currently used pediatric dose.

It is important to recognize availability of published clinical experience in adults and pediatrics for several of the drugs in opioid analgesic class, the clinical experience of which has been generated over the past several decades. It is also important to recognize several hospitals and professional societies have established guidelines to use some of these opioid analgesics in adults and pediatric patients experiencing pain due to different causes. So agency emphasizes the importance of conducting pharmacokinetic simulations prior to conducting pediatric studies,

be it PK studies or safety studies.

The goal of the PK simulation exercise is to identify dose expected to achieve an appropriate target exposure in the clinical context. The conduct of simulations prior to pediatric studies involve leveraging any available PK data from previously completed studies in adults. Most opioid immediate-release products have some amount of published data, both in pediatric and adult patients. Most clinical pharmacology programs dealing with opioid extended-release, long-acting products have traditional PK or population PK analysis plans.

From these, it is important to understand the physiological covariates, body weight, age, sex, etc [ph], that may help understand the variability in the pharmacokinetic parameters, such as clearance, volume of distribution, absorption rate, constant, et cetera.

Conducting simulations prior to pediatric studies involves use of PK parameters for pediatrics that may be estimated from adult PK

studies. It is important to check if the opioid immediate-release or extended-release products might have similar PK as it relates to adolescents and adults. It is also important to consider practice-based guidelines established by pain societies and hospitals.

In the next few slides, I'll describe an example of an opioid A where the assumed adult dose is 0.15 milligrams per kilogram, and it's given by oral route according to the product label. The underlying assumptions for the simulations include that the pediatric data is available for opioid A in publications mainly, and there may be some past clinical experience from the NDA program.

The assumption is also that data is available on clearance, volume of distribution, and for the oral route, there is some information about the absorption rate constant. For this particular opioid A, body weight is a very important covariate in that it explains significant inter-individual variability and that the relationship between body weight and PK parameters is curvilinear. It's not

to be assumed linear all the way.

Simulation scenario A, shown in this slide, describes pharmacokinetic profile of opioid A given orally every 6 hours in a 70-kilogram adult, represented by the red line, and pediatric data for 35-kilogram and 15-kilogram pediatric patients is represented as blue and grey lines.

As it happens, in this simulation, the dosing in pediatric patients will result in significantly lower exposure in terms of peak plasma concentrations, minimum plasma concentrations, and the area under the curve. Obviously, this scenario indicates that the pediatric dosing may not be optimal, or we are underdosing pediatric patients in this simulation.

Scenario B is a simulation representing pharmacokinetic profile of oral dosing of opioid A every 4 hours in adults, again indicated in red line, and blue and grey lines represent 35-kilogram and 15-kilogram pediatric patients, respectively; whereas the adults received 0.15 milligram per kilogram dosing, the pediatric patients received

0.3 milligrams per kilogram dose of opioid A.

In this simulation, the dosing of pediatric patients will result in minimum plasma concentrations that are comparable to that noted in adult patient simulation. Again, the goal here was not to match perfectly the Cmax or the peak plasma concentrations, or the area under the curve, but to get the plasma concentrations into the range known to be safe in adults.

Simulation C is a small variant of simulation B, where instead of 4 hours, the dosing regimen for the oral opioid A is every 6 hours. Again, the red line indicates adult data, blue and grey lines indicate pediatric patients 35 kilograms and 15 kilograms receiving 0.3 mg/kg. In this simulation again, the dosing in pediatric patients will result in minimum plasma concentrations that are comparable to that noted in adult patients.

This is an interim summary just on the simulations. Pharmacokinetic simulations can help support selection of at least the initial dose of opioids. Again, there are several important points

to consider before applying and going forward a lot with these simulations.

Most opioids in the market have some clinical experience published, and it's important to ask oneself, is there clinical experience with this opioid IR or extended-release product at the dose supported by simulations? In other words, are there reasonable differences across the United States, different hospital systems, in use of a given opioid and in terms of specific pain conditions, be it post-op pain or be it cancer pain?

Multiple dose PK and safety study protocols can employ continuation of the same initial dose; or titrate upward with the higher dose for managing pain if the pain management is inadequate; or the downward titration may be implied for reduction of any adverse events.

As described by Dr. Galati, age is one very important consideration also for clinical pharmacology when designing studies. For immediate-release opioid products, pediatric

patients 2 to 17 years of age are recruited for PK-only studies where extrapolation of efficacy is allowed. For PK assessments in birth to 2 years of age, it's only applicable to opioid immediate-release products. Opioid extended-release products, again PK can be generated for any given opioid 7 through 17 years of pediatric patient age.

It's very important to go into sample size calculation. I will spend another minute in the next slide. The number of blood samples play a very critical role in pediatric PK studies.

As it relates to population PK, it's important that blood sampling be justified using a sparse sampling strategy, which is aimed at minimizing the number of blood draws. And again, the sampling strategy in case of population PK analysis should adequately identify a blood sampling scheme that will capture absorption characteristics. This aspect is very important for extended-release opioids. In addition, it's important to also target samples that can give a

clear idea about the clearance and the volume of distribution of the opioid.

When it comes to traditional pharmacokinetic plan, justification of timing of blood samples during absorption, peak plasma concentrations, and elimination phase should be based on adult PK data, or any other known prior information.

As I mentioned before, the sample size calculation is something very important because the simulations are only as good as the parameters derived.

The technical statistical considerations around how to go about assessing precise PK parameters is described in a 2012 publication by our FDA colleagues. It discusses the methodology and consideration for pediatric PK studies. The main emphasis is on the characterization of clearance and volume of distribution. And absorption rate constant may be important again for opioid extended-release products, or for that matter, immediate-release products as well.

For single-dose PK studies, PK evaluation of

a single dose of an opioid immediate-release or extended-release product may be connected. It's very important to see and assess early on if the opioid immediate-release or extended-release PK is linear and dose proportional in adults. And thereafter, the single-dose PK predictions of multiple-dose PK should be done. And the single-dose PK data must be used either by nonparametric superposition or compartmental methods to predict doses required in pediatric patients to achieve plasma exposure comparable to adult subjects.

In multiple-dose studies, pediatric patients that will require opioid extended-release products for more than 2 days may be dosed up to steady state, as known in adults. The goal of such a multiple-dose PK study is to confirm that the dose selected in pediatric patients will in fact achieve plasma exposure of the opioid that is comparable to adults.

After the conduct of the PK single-dose or multiple-dose PK studies, the safety study should

utilize the doses derived from the methodology described before. The sponsors are recommended to follow the above paradigm and submit the information to justify dose selection prior to conducting any study. And these safety studies must include additional clinical safety considerations laid out in previous presentations.

I thank you for your attention and happy to answer any questions.

Clarifying Questions

DR. BROWN: Thank you, Dr. Nallani, for your very nice presentation.

At this point, are there any clarifying questions for the FDA concerning any of the presentations that we've heard this morning? Dr. Higgins?

DR. HIGGINS: I understand enrollment is a serious concern for this population, but I'm wondering, for either of the presenters, to what extent, to your knowledge, of the use of sampling techniques that are innovative and novel, such as sparse sampling, scavenger sampling, dry blood

spot, or any of those kinds of types of sampling methods, would make it more efficient to study this patient population?

DR. NALLANI: Srikanth Nallani, FDA. We in the Office of Clinical Pharmacology have a large amount of experience in population PK analysis with a variety of drugs, be it new molecular entities or previously known drug molecules. So the population PK analysis methods, particularly when they are well-identified in adults, they can well inform the pediatric sampling.

Specifically, the population PK analysis plans, they offer the advantage of very limited number of blood samples. These blood samples that are identified from the analysis plan will only target -- will only be arrived at because they have been known to predict the clearance of the volume of distribution of the drug precisely in the existing data.

Does that help answer your question?

DR. HIGGINS: I guess I was just more curious to what extent more novel techniques are

being used as a way of combating the fact that there's such low enrollment or low recruitment for this patient population.

DR. NALLANI: I recall you mentioned dry blood spots. They may be allowed. The only caveat to that is, the bioanalytical validation of such novel methods must be done simultaneously during the adult program. And only when they are known to be representative of actual blood sampling, without any confounding factors, it's hard to apply such novel techniques to pediatrics.

If such a validation, or a cross-validation, is done for, say, dry blood spots with human plasma PK, which is the conventional form in adults, we definitely encourage sponsors to do that prior to applying it in pediatrics.

DR. FIELDS: Ellen Fields, FDA. Dr. Nallani, correct me if I'm wrong, but we do encourage the use of sparse sampling and population PK in the pediatric studies. Correct?

That's what you were asking, right?

DR. HIGGINS: As well as scavenger sampling.

DR. YAO: Well scavenge is a different, is a whole different --

DR. FIELDS: I'm not familiar with that.

DR. YAO: Yes. So as we have come to learn, and in certain situations, the idea that you would have opportunistic sampling, or the scavenged sample -- in other words, a patient's getting a drug per standard of care, you collect some blood when they were going to get a routine blood draw anyway. And then you can take that blood, whether it's a dry blood spot or whatever, and then analyze that to get more information on the pharmacokinetic profile.

The problem with the scavenged sample, and why we don't necessarily always use that in settings where a PREA study or a drug company sponsored study is going to be undertaken, is that in the use of scavenged samples, you have to rely on the time at which the drug was given, and then know how further or later that routine blood sample was obtained.

And many, many times, as you know, when

you're working in the hospital, the drug administration will be rounded off to the closest half hour or hour. So there's not necessarily the greatest correlation or the most precise dosing interval when we're getting those scavenged samples. So that's not to say that we couldn't use them, but oftentimes we would not rely on them as the primary data source to characterize the PK.

DR. XU: This Yun Xu from Office of Clinical Pharmacology. I just want to add one thing, saying that we will compose either sparse sampling or for PK sampling. The main purpose is try to either measure so to accurately characterize the PK parameters in pediatrics to allow us to do the PK matching approach over here.

I think in Dr. Nallani's slides, there is literature by Dr. Wong talking about how to design a PK study in pediatrics. So either PK or sparse PK sampling should follow the guidance in that specific literature to select PK sampling appropriately.

The second part for the dry blood sampling,

I think we will certainly encourage that, but before the sponsor considers the dry blood sampling method, they need to show us that the dry blood sampling method will have the same accuracy as the traditional 4-blood draw method. Usually in that case, we will require the sponsor to conduct a comparison study in adults comparing 4 blood sampling and also dry blot blood sampling to show that these two methodologies will have the same values. So after that validation, then the dry blot blood sampling may be used in pediatrics.

DR. BROWN: Dr. Emala?

DR. EMALA: Charles Emala for Dr. Nallani. It's actually a related question on slide 6 of Dr. Nallani's presentation. It seems like a little bit of circular reasoning, because the slide says, in defense of simulations, that the simulations should be started prior to actual pediatric PK studies. But under the bullet point, the second bullet point, the assumption is that pediatric PK data is actually available.

So is it perhaps more appropriate to say

that the simulations can be useful to predict further refined pediatric PK studies, but not necessarily can take place before an actual study has occurred?

DR. NALLANI: Yes, I did anticipate that question. Yes, what I have described here, it is in the paradigm of learn and confirm. And for several opioids, not all of them, there is limited PK data in certain pediatric age groups. When looking at such limited PK data in certain limited age groups, and again considering the limitations of how the pediatric data is described in publications, hardly any information is given to us as it relates to bioanalytical validation.

Yes, there are some mentions of the analytical method, how it's done, but they don't rise to the level of how we scrutinize data when it comes to us. So that doesn't mean the data is not useful. It's just that it's a starting point in the learn and confirm model, as you mentioned.

So such PK data may be used in the simulations. Again, after the simulations, we have

to then see how the dosing arrived at is already -- whether there is some clinical experience or not, particularly since there is significant clinical experience with opioids.

DR. BROWN: Dr. Crawford?

DR. CRAWFORD: This question is for Dr. Galati. It is based on your slide 4, pediatric assessment post-marketing requirements from PREA studies that list the opioids with pediatric information in the labeling, on the top. Some of these are by the generic names and some are by specific products.

My question would be an example of the one hydrocodone and acetaminophen, which lists one product. Hydrocodone containing products got a lot of attention and interest with FDA actions in 2014. Would that mean that any other branded or generic hydrocodone and acetaminophen products with pediatric information that were prescribed for pediatric populations would be considered off label? I'm trying to understand the outreach of PREA because I just see one listed, and we know

there are many.

DR. FIELDS: Hi. It's Ellen Fields from FDA. So that language is specifically in -- it's a generic product, the Lortab tablet. It is not in -- and that's an oral solution I believe. It might also be a tablet. But it's not in other -- I'm sorry, which one were you asking about?

DR. CRAWFORD: You were correct, that's the one, Lortab hydrocodone and acetaminophen.

DR. FIELDS: Okay. Right, it's not in other hydrocodone products, either because the way they were approved would not have linked them to that product, so they would be considered off-label.

DR. BROWN: Dr. Fields, could I ask for a little bit of clarification in that? In other words, other hydrocodone and acetaminophen products would be considered off label?

DR. FIELDS: Yes, if it's not in the label. And I believe the dosing instructions are only in the Lortab label. I've looked at it several times. Like hydrocodone/acetaminophen tablets, Vicodin for

one does not have pediatric dosing in it.

DR. BROWN: There must be reasoning behind that.

DR. FIELDS: Well, it's a regulatory reason I believe because of the way they were approved and what they were linked to. And Lortab is a very old drug. I don't exactly know how they got that pediatric dosing language, but there must have been some basis for it for that product. And other products have not either linked to it in a regulatory sense or done any studies. They are all old products.

DR. BROWN: And that's their choice to not --

DR. FIELDS: Well, if they're old products, they're not required to come up into compliance with PREA if they were approved prior to a particular year; that Dr. Yao probably knows.

DR. YAO: And let me just clarify a little bit. So the slide describes opioids that have pediatric labeling. Just to clarify, it doesn't mean that the pediatric labeling came from studies

that were required under PREA.

Much of this information is old, and if we were to look at it, we might agree or disagree that the strength of evidence that we would require now is there or not there. That's a larger issue that we're dealing with at the agency about improving old labeling, even labeling that's not even required to convert to physician labeling rule.

I just want to just make sure that the committee understands that distinction, that the labeling that's here about pediatric information may not in fact be related to -- may not be a consequence of studies that we required under PREA.

DR. BROWN: Dr. Cnaan?

DR. CNAAN: Avital Cnaan. I have two questions for Dr. Galati, one on slide 17. You say that ages zero to 7 for the extended release is waived due to low prevalence. My question is, does it tie or does not tie at all to any regulations that have to do with rare diseases?

The second question is in the consideration for study design, and in mentioning the various

diseases again about extended releases, it does not mention anything about use of extended release for palliative care. Is that some of the considerations?

DR. HERTZ: This is Dr. Hertz. The approach to rare diseases is not part of this waiving. So the use of extended-release formulations in patients under the age of 7 based on our approach to studying them, it generally requires several weeks of treatment, and it's really not feasible to find a population to study. And that's why it was decided to waive it. It's not that it's not important information for the few cases where it's necessary, it's about whether or not the studies can even be conducted.

We tried for a number of years to get a variety of studies done for opioids throughout the full pediatric age range, and they just weren't able to be completed. Enrollment was not sufficient to support meaningful conclusions or collection of data when it comes to certain types of products.

So in this case, for the extended-release products, we waive the requirement to do PK and safety data in zero to 7. We do collect information about the moiety when we get studies for the immediate-release products, and no age group is waived in that setting.

DR. FIELDS: And do you answer about the palliative care? Oh yes, palliative care would be an area where we would be willing to enroll patients for chronic studies.

DR. YAO: Can I just add one -- I don't want to stray too far off topic. But I didn't make a big point of this, but under the law, if you have received orphan designation, because you're studying a product for a rare indication, actually currently the law says that you're exempt from PREA requirements. So there's also this issue here about what PREA can actually be required if you're intending to study a rare or orphan indication.

DR. BROWN: So would you consider chronic pain in children under 7 to be a rare indication?

DR. HERTZ: No, we don't consider pain to be

rare, which is why --

DR. BROWN: Chronic pain, chronic pain in children under 7.

DR. HERTZ: I don't know that I can say whether we consider that to be rare. What I can say is that we consider that it's not feasible to conduct the studies with the number of children that can be enrolled in studies.

So we're not making a determination of it being rare or not. We're just saying that it's one of the -- we can require whatever we want, but if the studies aren't feasible, and companies try over and over and over again and are unable to enroll, then the requirements have no merit.

So over years, we have been trying to get certain data, and that's why in that setting we have come to understand that we're not going to get those studies; they're just not going to get done.

DR. BROWN: Dr. McCann?

DR. MCCANN: Mary Ellen McCann. I have a question for Dr. Galati. I believe it's slide 17 where you said for immediate-release agents, you

study ages zero to less than 2. What does zero mean? Does it mean term babies? Does it mean term babies plus 72 hours? Does it include premature babies?

The reason I ask is doing some simple math, I think 10 percent of births in this country are premature, and 90 percent of babies under 34 weeks end up in a NICU, and they all -- they don't all, but a fair percentage of them get treated with these medications for sedation.

So when I went through the paperwork, I was like, there's this huge unknown of how to treat these infants, and they're just a huge percentage of the care that we deliver as pediatricians is in that first month of life, and even more so if you're born premature.

DR. HERTZ: This is Dr. Hertz. We are aware of the clinical setting that you have described. In one of our early written requests, the written request that was generated for morphine sulfate, we worked internally with our division people in the division at the time that had pediatrics. We had a

neonatologist present at the time. And we wrote a very extensive written request that includes different categories of prematurity.

Nobody was willing to do that written request, none of the sponsors. And we have referred that written request to NIH, and as you know, there's still no information.

The idea of trying to conduct these studies in that age group is a classic example of the conflict where we need information, but it's extremely challenging to get it. For one thing, we are not comfortable, based on the information that we've been able to find in a variety of settings, to extrapolate efficacy in the most young.

Then we are challenged with understanding how to evaluate efficacy in the most young. And then understanding that the effect of a product like an opioid can be to provide analgesia, which would allow an infant or a premature infant to be comfortable and then sleep, is extremely difficult to separate from the sedating effects, which may also allow the child to sleep.

Then we have the complicating factors of the environment. The management of that child that requires NICU treatment. It's an extremely difficult population to look at clinical outcomes in this therapeutic area.

It's also even difficult to get PK data. The challenges that we face with parental consent for study participation in the entire age group becomes more and more challenging it seems the younger and/or sicker the child.

So zero means all of the potential categories that you've described. And when we think about the studies and what we're going to require, we are always forced to consider what is possible, but we have tried. I mean we have certainly tried to define different levels of maturity from less than 40-week births and tried to get some of that information, but it's exceedingly difficult.

DR. BROWN: Dr. Patrick?

DR. PATRICK: My question was very similar. Stephen Patrick from Vanderbilt. One point to

attach onto is, how is safety defined. And for particular that age group that we just discussed, does it extend to neuro developmental outcomes? I suspect that much of what -- the answer to that is similar to what you just answered.

DR. HERTZ: Yes, we do include developmental outcomes, including neuro development, as part of the safety collection for pediatric patients in these studies. Depending on the nature of the study, especially if it's a short-term post-operative exposure, we don't collect a tremendous amount of information.

But as you can imagine, understanding the impact of a period of treatment with an opioid and all of the other treatments, both pharmacologic and non-pharmacologic, the reason for prematurity, the reason for a need for surgery in early life, potential anesthetic exposures, exposures to other sedatives, it is -- I feel like using the word "challenge" doesn't even come close to the situation. But trying to sort out the influences of all the many factors that can have an impact on

long-term neuro development in a child in that setting is something that would require an enormous database, and we don't typically see that.

You may be aware that in our division, we're also very interested in the impact of different anesthetic agents or products used in the OR on the developing brain, particularly under the age of 3, based on a lot of non-clinical work. We have a public/private partnership that we work with.

So we're very heavily invested in understanding the effects of early life exposure to a number of agents. And opioids are within the realm of what's used in the OR, and more of that type of research is occurring in that slightly different setting, but still has the same value of extending to the very earliest exposures.

We have a lot of non-clinical work that either FDA or other agencies have funded. We have folks in our National Center for Toxicologic Research doing work here in appropriate models of the very young brain. And we are participating in discussions of how to design clinical studies to

capture the effects of these different exposures in children who require different procedures. So there is a lot of work going on with that, and we certainly recognize the importance.

In the context of using opioids in the NICU, in the setting of pain, specifically we don't currently have a clinical study of that nature going on, but it's all related in terms of what we need to know about the effects of these products.

DR. BROWN: Dr. Kibbe?

DR. KIBBE: Thank you. I have some PK questions. In general, opioids, when given immediately, have a similar half-life pattern across the class. You have data already on hand on a lot of the drugs in adults, and so you can get a consistent trend from all the data you've already gotten on the half-life, terminal half-life or the excretion half-life.

When you start to see that kind of data come in with your pediatric patients, depending on what age group, is there any change that you see that could be plotted against age to look at the

changing nature of the way the developing child handles the excretion of the drug? That's one.

A second, we generally believe that with a lot of drugs, you can establish a minimum effective concentration and get a result. But with pain, because pain is so subjective, you're on your own. But is there any data at all where we can see toxicity kick in, like respiratory depression? And then can we extrapolate that back to give the clinicians some kind of a safety window? Because I really think the bottom line, when all this is said and all this discussion we have, each clinician is going to have to deal with a patient, start them out with a dose that is reasonably safe, and titrate up to get the kind of relief they had.

When I was at NIH, we were dealing with end-of-life pain patients, and some of them were on 2 grams of morphine sulfate a day. And that is a tolerance issue, and it builds up over time. And I don't know whether you have pediatric patients who ever are on chronic pain for long enough to be in that situation, but that's another aspect of

converting from adult data to human data. So the question is about kinetics.

DR. NALLANI: So I can generally talk about how we approach the evaluation of pediatric PK. Over the past 10, 20 years, we have come to know that the specific pathways of hepatic metabolism are renal excretion or any other elimination pathway. They mature at different rates in pediatrics, and by a certain age they are comparable to what's known in adults.

So, the exact clearance of each molecule is defined by that particular pathway. For example, morphine is glucuronidated, and there are other molecules that are metabolized by cytochrome P450 3A4, and some are metabolized by cytochrome P450 2D6. So the maturation of individual enzyme A is different.

When we ask for pediatric PK studies and specify certain age groups, we take our prior knowledge of PK of different drugs in pediatrics, and then specify these age groups. So we cannot, in a general way, say that, okay, this is the

half-life of opioid A, so it will be the same for opioid B. We can't do that, but -- I'm sure you're not saying that, but basically at the planning stages, the guidance very clearly asks that sponsors take the maturation considerations around the absorption, distribution, metabolism, and elimination. So that's the PK part.

Now as it relates to the safety, we do -- yes, I'll let Dr. Hertz answer the --

DR. HERTZ: We don't have the information that you've asked for, which is the threshold beyond which we're concerned about safety. What we are trying to develop with the pediatric studies is what's a safe starting dose, so a slightly different question. But what's a dose that's likely to be somewhat effective and safe as a start, knowing that the opioids will need to be titrated to effect, and that there are many, many factors that will go into that; the existence of any prior opioid exposure and opioid tolerance, if it was to the same or a different moiety, other concomitant sedating drugs, depending on the

circumstance.

So what we hope to achieve with the PK studies that are done, which are PK and safety studies -- we don't ever extrapolate safety so we're always collecting safety information -- is to try and establish the appropriate starting dose.

The challenges that we've had in particular with that approach is we have to try and integrate the modeling and the initial dosing information that's going to capture some of the PK with the safety data. But because these are typically open-label studies, we also have to try and catch some of the outcome data to understand what the dose, the resulting blood level, and the clinical picture, how those correlate in terms of is that a safe starting dose.

For instance, if we have a situation in which there are children who are getting post-operative pain management and have a relatively simple set of concomitant medications, then we look at age appropriate pain instruments, different rating scales. They vary quite a bit by

age over the developmental scale until children are old enough to self-report pain reliably, typically in the older adolescents. And we also look at the use of concomitant medications for pain management.

So we try to look at a variety of things to put the exposure in context. So far, we haven't had a situation in which the starting dose was so high that the study had to be discontinued and reconfigured to a lower dose.

What we did have, one experience so far, in which the initial planned, or the dose that was used in the study, produced much lower than expected exposure relative to adult exposure at the lower doses. Unfortunately, that study did not collect enough additional data. For some reason, the information about concomitant meds was lost, so it was very hard to put that in context.

So we know that dose is safe, because we didn't have safety concerns. We just don't know if it's a reasonable starting place. So we're going to be doing -- that sponsor's going to be doing some additional work.

The approach we take is to use the published information, clinical practice guidelines in different settings, the simulation data that's available, information about human exposure, all of these things, as Dr. Nallani described, that go into the initial modeling and establishing the PK.

We try to get some pilot studies if we can to make sure that these assumptions are leading to an appropriate dose. Then our target for the opioids is a safe starting dose that would then be used to titrate to the desired effect in a closely monitored setting.

DR. KIBBE: Back to the very beginning specific question which I had, which is say for oxycodone, if you know the half-life in mature adults because you've gotten biostudies, you've got all sorts of -- have you been able to look at the terminal half-life of oxycodone in different pediatric groups, and is there a trend?

Is there a discernable way of looking at that as a guideline for what you want to do in terms of dosing regimen, time between doses, things

like that?

DR. XU: Specifically, as it relates to oxycodone, yes, we do have some information. Now, how that relates to the -- what I can say is, the PK data that is available for, say, immediate-release oxycodone is only to the level where we can then go on to do a safety study. We don't have enough data to label the products.

Does that answer your question?

(Dr. Kibbe gestures - no audible response.)

DR. HERTZ: But I can answer it with a non-opioid, because we have some parenteral formulations of non-opioids that have undergone extensive pediatric evaluation. And there we've been able to look at the pharmacokinetic profile across a variety of age spans, to look at the changes in exposure for a given dose.

Ideally, that was a much more modern program because those products are much newer, and they fell under the requirements of PREA, so we were able to require quite a nice range of studies that were very informative. We knew that there was a

need for use of those products in this population. So we got a very nice span of PK data across ages, not all of which was what was expected, which was why it underscores the importance.

So yes, when we have the opportunity to require the studies, the idea is to do exactly what you've asked, to get a range of PK characteristics to inform appropriate dosing over the whole age span, and see how the metabolism and exposure behaves across the whole pediatric age span.

DR. BROWN: Dr. Kaye, do you have a comment on this?

DR. KAYE: Yes, just from a pharmacologic point of view, and taking aside different chronic diseases that may affect physiology and pharmacology, there's reduced absorption, metabolism, and elimination. And to Dr. Kibbe's points and comment and question, there is data with glucuronidation, like with Lamictal in children, and at, say, age 6, it's reported at 14 percent compared to adults, and down to zero or 1, all the way down to 1 percent.

So it's not linear, and that's why this is so important. Hydromorphone, oxymorphone, morphine, are all glucuronidated as examples. So even if you add all the pharmacology that we know, it's scant overall if you look through the literature like they have, and like many of us have in different ways over the years.

DR. BROWN: Dr. Havens?

DR. HAVENS: Thank you very much. So it sounds like when there's appropriate PREA requirements, you are able to get sponsors to deliver data performed in an appropriate way. As you just said, PK over a wide range of ages, which give you some surprises. But then it sounds like for many of these older drugs, you're not able to force sponsors to do those drugs for whatever reason, and there may not be enough patients available in single-center studies to be able to do that.

The rest of this conversation, it strikes me as what do you do when you can't do the right thing? You say that you can do the right thing

with PREA demands, and it can work. And so the patients are there.

I'm struck in the backgrounder, table 3 on the duration of therapy has over 1.6 million patients in 2015 alone. There are many other drugs that are developed for treatment of diseases in children, many fewer than these, that depend on consortia developed or supported through the NIH, for example. So the question would be what has been done to try to develop these kinds of consortia? Many groups have them, emergency rooms, critical care, cardiac surgeons; all these people have different practice consortia, in oncology.

So why can't we put together a consortium of groups that would allow the appropriate studies to be done by somebody other than the sponsor, perhaps supported through NIH or other agencies?

DR. YAO: Lynne Yao. I think I can answer that, help answer that.

DR. BROWN: Please do.

DR. YAO: Oh yes, please. Please I'll go.

DR. WALCO: Gary Walco from Seattle

Children's. So we actually got funding about four years ago to start a group called PRN-Pain, Pediatric Research Network for Pain, which also became part of ACTTION, which is a public/private partnership with the FDA. We have 35 institutions who are onboard and are perfectly willing to party with us. And you'll be shocked to know that the limiting factor was funding.

When we went to NIH, their response to us was do some studies together, do a series of studies together, and then eventually we can look at you as a consortium. Pain is not a disease, so when you look at the other groups that you've talked about, like the Children's Arthritis and Rheumatology Research Alliance, they got their major funding through the Arthritis Foundation.

When you look at the Children's Oncology Group, they had what I think is a once in a lifetime opportunity with the War on Cancer that Nixon started back in the '70s and the huge amounts of funding. When you look at the Cystic Fibrosis Network, they basically grew out of another

charitable base plus partnering with drug companies.

We've looked at this several different ways, and I will also throw another log on the fire and say we did look at partnering with industry because that's a source. And if you want to risk your career, you'll do opioid studies and take money from drug companies in the current political environment.

So it's not that it hasn't been attempted, and the network is still there. We're still trying to move it.

DR. HAVENS: Well, you've answered the question. Specifically, until there's the political will to do the studies the right way, then we're going to spend a lot of time trying to figure out how to do something other than the right studies.

I do a lot with HIV. There's big NIH supported networks that have been existing for many years, not through private foundations but only through federal funding. And if some of this is

related to the panic about opioid misuse and addiction, then this might be a time when the political will could exist to do the right thing at the federal level.

DR. WALCO: I would wholeheartedly agree with you, and I will also very quickly point out that the CDC guidelines that came out on this topic systematically excluded everybody under the age of 18. And the National Pain Strategy that came out in March of 2016 likewise completely omitted pediatrics.

So I think your points are spot-on, and at this juncture I don't see that much. I mean, hopefully this meeting will help spawn that kind of awareness to actually get people to see that pediatrics is a group that needs focus for these issues.

DR. BROWN: I would also say, for the folks in the audience from the American Academy of Pediatrics, that this is a wonderful opportunity for 75,000 pediatricians in the United States to get heavily involved in pushing this at the federal

level.

Dr. Neville?

DR. NEVILLE: My question was for Dr. Nallani. And forgive my ignorance, but I understand the reasons and the benefits of sparse sampling, but can you comment on how that would affect sample size when you're extrapolating from adult studies? Because what I'm thinking about is the rarity of chronic pain and the difficulties in accruing to those studies. And I know it's related to variability, but my concern is it would increase the needed sample size.

DR. NALLANI: So the publication, the pediatric draft, pediatric clinical pharmacology guidance, and the Wong 2012 paper in the Journal of Clinical Pharmacology, specifically address how to go about making assumptions and arriving at the number of subjects you'll need, be it if you take a traditional PK approach, or be it if you take a population PK approach. It requires that you assume in specific age groups that the variability of data is by a certain percentage of standard

deviation.

So for opioids, I will not say that, okay, so this is the percentage of standard deviation in all adults for all opioids. But if you look at the publication, it clearly discusses different scenarios of assuming, say, 20 percent CV through 80 percent CV. So if you assume the variability only in PK is, say, 20 percent, you can recruit as little as five subjects in that particular cohort of that age group.

Of course as the variability increases -- where I'm coming from is, the smaller your age cohort, the better you'll be able to explain the variability as it relates to body weight or changes in age and gender differences.

DR. NELSON: I guess I'm asking more, A, specifically about the long-acting opioids, and B, most of the studies are designed in a wide age group. So my concern is less time points from each patient's will then confer a higher number of needed patients.

Is that accurate or no?

DR. NALLANI: So for extended-release, long-acting opioids, we only go down to the age of 7 years. For adolescents, again, you can't generalize it to all extended-release products, but classically what we know is for adolescents, say 12 through 17 years, the pharmacokinetics of drugs tend to be similar to adults. So then you already know what the variability that you expect.

DR. NEVILLE: But that's 12 to 17, right?

DR. HERTZ: I think the answer is yes. Yes, we do get an impact in terms of understanding the number needed to enroll in a study versus the sparse sampling and all that. But, don't forget, a lot of our studies that are being done in this setting, because we're extrapolating efficacy and we're just relying on new data for PK, we're also collecting safety data. And the number of patients that we need to study to get a safety profile is generally going to be quite a bit larger than what we need, even in a sparse sampling PK population.

In fact, sometimes we will only have the sparse sampling at some centers or some -- not even

the entire study population, just at certain sites, because, again, the number that are enrolled to get the safety data generally will exceed the number needed for the PK data.

But also what we do when it's possible -- and again, we don't have a ton of experience with these pediatric programs, but we try to get first basic information about the moiety. So before we jump into an extended-release study, we want to know what the basic pharmacology is of the opioid, or pharmacokinetics of the opioid is, and then we can look at it in the extended-release formulation.

So sometimes the pilot studies will be with an immediate-release product so that we -- we want to make sure that when an extended-release product is dosed, which you know if the initial calculations result in a higher than expected exposure, we certainly don't want that to be in the context of dosing an extended-release product. It's much safer to start with an immediate release, shorter acting, where we will have the ability to

not have as long period of that high exposure.

For instance, in the OxyContin program, there were studies that preceded the actual study of OxyContin using other formulations of -- immediate-release formulations of oxycodone. So we established some basic data that informed the dosing considerations for the extended-release formulation.

So that was the groundwork, the pilot work, to even embark on a study of a extended-release product at all.

Then what we then had to look at -- well, actually I'm getting a little off topic. There are then other considerations for what is done in terms of dosing based on the formulation issues with any given product, how small of an extended-release dose can be created. And if that dose is too large to accommodate the expected dosing for the age range, that initial safe dose, we may have to change the enrolment criteria.

For instance, the lowest available strength of OxyContin was higher than the predicted starting

dose based on the pharmacokinetics of oxycodone. So all of those patients were required to have met, through use of IR, the requirement for that minimum extended-release product. If you're not already tolerating that minimum dose, which is 20 milligrams a day, and in fact need that much and tolerate it, or more, then you weren't even going to be enrolled to get the PK of the ER.

So there are a lot of factors that go into it, but basically, back to the original question, the numbers needed for the PopPK, even though that type of methodology may increase the overall number, is still dwarfed by the safety numbers.

DR. NELSON: Thank you.

DR. BROWN: I think at this time, we're going to break for lunch. We will have time after lunch for further questions. I know there are some folks that haven't gotten their questions in, and I want to make certain that everyone has a chance to ask their questions and give some discussion.

We're going to reconvene again in this room in about an hour, maybe at 12:45 or 12:50. Please

take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussions of the meeting during lunch with the press or with any member of the audience. We'll see you back in an hour.

(Whereupon, at 11:50 a.m., a lunch recess was taken.)

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

(12:47 p.m.)

Clarifying Questions (continued)

DR. BROWN: We're going to adjust what we had planned to do and have about 15 more minutes of clarifying questions since we have a whole list of people that want to speak.

We likely will not get through these. We'll still have a section of clarifying questions at the end of the day, after all the speakers have had a chance to talk. But at this point, I'm going to give Dr. White an opportunity to ask his question.

DR. WHITE: Thank you. Regarding the PK studies, we're looking at small populations and small age groups. How are we going to account for the CYP2D6 polymorphisms and ultra-metabolizers and such using these small sample volumes considering the ethnic variation that one sees in the expression of the ultra-metabolizers? Does anybody have a plan for how to approach that?

DR. HERTZ: This is Sharon Hertz. It looks like our clin/pharm folks are not quite back from

lunch, so I'll give --

DR. WHITE: We can address it later. That's fine. We'll do it later in the day.

DR. HERTZ: I can give it a shot, in just that I think we have been asking for typing in some of these studies where it's relevant. We wouldn't want to base labeling on a sample that in particular ended up enrolling folks with a number of the either extensive or poor metabolizer phenotypes. So I think we do typically screen for that.

We are dealing with the 2D6 polymorphisms in a number of ways right now with regard to pediatric analgesics in general. So we are thinking about them in a broad sense for the drug substances in which it's an active concern.

DR. WHITE: Thank you.

DR. BROWN: Dr. Maxwell?

DR. MAXWELL: I'm Lynne Maxwell from the Children's Hospital of Philadelphia. I have a PK question and an ethics consent question. With regard to PK, in some studies the protocol

specifies that blood must be drawn from a venous line and not from an arterial line. And I wondered whether this is based on data on drugs in general, or opioids in particular, and whether this guidance comes from the agency.

The ethical question I have, having to do with consent, is the issue of drawing blood from central venous lines in an era where there's so much concern about accessing lines and central bloodstream infections, and whether that needs to be specified as an additional risk in the consent process, because we've had problems with caregivers in ICUs who were reluctant to have their patients enrolled in studies in which the PK samples and safety samples have to be from additional draws and not scavenged serendipitously.

DR. BROWN: Dr. Nelson, I know you just got back, but this question from Dr. Maxwell relates to an important ethical issue. And Lynne, if you could just summarize that last question you asked so that Skip can have some time to speak to that?

DR. MAXWELL: So whether the potential for

drawing blood samples from central venous lines is enough of a significant above-minimal risk to be specified in the consent.

DR. NELSON: Skip Nelson. In thinking about it, I think the question would be if in fact the risk can be specified. So I know that the risk of a catheter -- CLABSI I guess -- catheter-related acute, whatever it stands for at this point, if it's still true related to the number of ports, related to the number of times you go into it, and so on and so forth. I think if in fact that's the case, then if you can quantify that it's a risk that ought to be mentioned.

Now, the challenge would be to the extent -- I mean, Lynne had earlier mentioned, Lynne Yao, the issue of scavenged samples and timing. I think if one knows when a drug is given in a more specific way than just found, for example, in nursing notes, and can time a sample, and you're doing PopPK and not a more sort of timed analysis, then you could perhaps overcome that and combine it with sampling that's being done at the

same time, in which case the additional blood is pretty much a minimal risk since the risk is related to the actual insertion itself.

So a lot of it comes down to the design and whether or not you've got the technology to do the time collection in a way that means the data are in fact useful.

DR. MAXWELL: That's certainly what we try to do, but there have been concerns expressed by especially caregivers in ICU about additional blood draws.

The first question was about any known differences between plasma levels of drugs in arterial versus venous blood samples.

DR. HERTZ: This is Sharon Hertz. I don't know the answer to that. We'll have to check when our clin/pharm folks return.

DR. MAXWELL: Because when we've tried to push back, because it's certainly easier to draw blood from small infants from arterial lines than from venous lines, companies have told us that either they don't know if there's a difference, so

they don't want to have diversity in the samples when there might be a difference, and I was wondering whether there was evidence that we could martial to contest their contention.

DR. HERTZ: That's not a typical point of discussion for us. We don't have a standard where we say the blood should be from a particular type of source, venous or arterial. But I'll check with them in terms of what we know about possible impacts on levels.

DR. MAXWELL: Thank you.

DR. BROWN: Dr. Turer?

DR. TURER: Thank you. My question has to do with in terms, particularly with the simulation modeling, and then using weight-based dosing, if we know that that's the best way to dose these drugs. And the area that I work in with pediatric obesity, we have 1 in 3 kids that are overweight or obese. These kids, particularly when they undergo tonsillectomy and adenoidectomy, are having difficulty getting extubated. We have had deaths in fact from the use of some of the opioids.

So I have concerns that we don't know a lot about should we be weight-basing these? Should we be using BSA? Should we be using ideal body weight adjusted BSA? And in those simulations, I think it would bear thinking about putting in ways to control for those things, or evaluate their impact on efficacy, safety, particularly in these patients who may have different volumes of distribution, and maybe impacted differentially even by the type of drug that we're using, whether it's lipophilic or not.

DR. BROWN: Dr. Czaja?

DR. CZAJA: I just had a couple of questions about the simulation work, and it kind of goes along the same lines. How much do you account for presence or absence of chronic disease when you do the modelings, so things that are going to affect the clearance?

Then you were saying that when you target your ultimate plasma level, it's based on adult demonstrated safe levels. And I was wondering what type of data informs that that's a fair assumption

to go from adult to pediatric safe plasma levels.

DR. NALLANI: So the first question is how does the chronic disease affect PK? That is a question that we ask at the time of the NDA review for adults. And we do try looking at PK of the drug in otherwise healthy subjects in a PK study, versus what happens in chronic pain or acute pain PK/PD type studies.

In my limited experience, what I can say is unless these disease changes have actual effect on the absorption, distribution, metabolism, and excretion, unless they actually directly modify these, we seldom see a difference of actual disease on the PK as such. That's the first thing. So yes, we do try understanding what the effect of disease is on the PK.

Pardon me, but can you repeat the second question?

DR. CZAJA: You were just saying that when you do your simulation studies, that what you're aiming for is what is the known safe level in adults. And I was wondering what data you used to

say that's a fair assumption to translate that to pediatrics.

DR. HERTZ: This is Sharon Hertz. There are a variety of factors that go into the initial pediatric dose. The rationale for targeting the starting dose in adults is we don't generally have identification of a true minimally effective dose, but we do know from most of our opioid programs where we start to get an effect, and we do generally have dosing that's consistent with pretty much the lowest reasonable dose as a starting point in an opioid naïve patient.

In terms of understanding if that's a reasonable target, you've heard that while in some circumstances we are extrapolating efficacy, we don't extrapolate safety. So there is not affirmative evidence to say that if a starting dose is absolutely safe in an adult, it will absolutely be safe in similar exposures in a child. But because of the general information we have on existing standard of care paradigms for dosing, and the available literature, and then the data that we

have for some products, we generally get a sense that that's true. But that's why we don't -- because we can't simply assume it's safe, we actually have to study it.

So that's why we say, it is not acceptable to extrapolate safety, we actually have to dose the product and confirm safety. So if there is any question based on any source of information that the target dose, based on adult, would not be appropriate for children -- for instance if the calculated starting dose for the pediatric study is larger than what would be found in standard of care, either textbooks or local practice, we would certainly not require that those standards be exceeded, and we would adjust the dosing accordingly.

So we don't know it, but we try to use a variety of sources of information to confirm that it is a reasonably safe starting dose. And then of course, the children are going to be monitored. This is not typically something that's going to be done in an outpatient unmonitored setting in these

early PK studies.

DR. BROWN: Dr. Flick?

DR. FLICK: Dr. Patrick and Dr. McCann earlier talked a little bit about definitions. And as we think about how we're going to do a better job of gathering data and being able to compare that data between studies and across populations, one of the things that I think is important is standardizing definitions.

Could you go to slide 17 I think it is? So in slide 17 it --

DR. BROWN: Randy, which presentation?

DR. FLICK: The last one, whatever. It doesn't matter. So --

DR. BROWN: Dr. Nallani's?

DR. FLICK: Yes, the age groups.

DR. BROWN: Seventeen.

DR. FLICK: There are differing age groups. If you go to the draft guidance for industry in your briefing book, page 42 of 108, that also -- and then two pages later -- or I'm sorry, page 55 in the draft guidance, there's differing

age definitions in all of these areas, which makes it very difficult to design studies and have studies that are comparable from one to the next.

I wonder if it would be helpful -- in fact if you look at the briefing book on page 42, infants are defined there, and this is that CDER generally divides the pediatric population to the following groups and defines infants as 1 month to 2 years.

No one defines infants as 1 month to 2 years, which makes it very difficult to compare any data that are collected that way with data that are collected with standard definitions of what an infant is. And then subsequently, there's a different age breakdown.

So I wonder as we think about this, and we think about how we're going to do a better job of collecting data going forward, that we use standard definitions and consistent definitions over time.

DR. HERTZ: This is Sharon Hertz. I just want to respond to the question I heard in there, sort of very deep. The ages conveyed in the

current slide are not the ages that are typically used for study enrollment. They just reflect what the general approach is for information gathering with regard to whether or not efficacy is required or whether it could be waived.

What our usual approach to defining age within a study protocol, or in fact when to split studies into different protocols, is based on a couple of factors that I still think could benefit from your suggestion when applicable.

So for instance, if we're collecting efficacy data, even if it's going to be -- well, when we're collecting efficacy data, it's very hard to mix different scales from different age ranges in the same study and have something that can be analyzed in a meaningful way.

So verbal and non-verbal is often a cutoff and the ability to respond to different scales, where that's an important element of the study. The clinical setting of where the patients suitable for the treatment will be found may differ based on age, so that might be another dividing point for

clinical study age enrollment.

So there's a variety of things that go into it, and also the expected maturation of the metabolic path, and that will be part of it too. So there are a number of different things that may create some degree of variability, but as folks discuss the questions tomorrow, that would be nice to have. In the absence of specific factors that might create some variability when those factors aren't in play, what are age ranges that make sense to this body?

DR. FLICK: Well, Sharon, I think we also have to keep in mind that some of the things that we -- when you're looking at safety data in the setting of a particular disease, the data or the literature on those diseases is gathered in using age groups that are sort of standard. And to be able to compare the safety data with disease incidence or prevalence data requires that you have standardized definitions.

DR. YAO: I'll make a comment about that too. This is Lynne Yao. So I think we are in

agreement with you that there's a, I think, increasing recognition across pediatric practice that actually age is probably a very poor surrogate marker for many, many different things. We have relied on it historically because it's very objective and very easily measured, but may not reflect really what is the important characteristic of the patient that needs to be measured against. So I think your point is very well taken. We understand that.

Please understand that the regulatory definitions that we provide are oftentimes sort of mixed up within what the scientific bounds would need to be in order to study the product or run the trial successfully. But those regulatory definitions are really intended to be there, I'll say, to ensure that the entire range of pediatric patients is addressed in whatever development program.

So we should not take that to mean that, well, if FDA said it's 1 month to 2 years, that that's all we really need to study if we're

studying infants, or that it would be something more or less than that.

I just want to just make that clarification, that how we decide we're going to study something, evaluate it, could be very different than what age ranges are described in a guidance or statute to cover the pediatric population.

DR. BROWN: Dr. Hudak, I'm going to give you the last word before we move on.

DR. HUDAK: Okay. Thank you. This gets back to Dr. Pham's presentation this morning. And my take-home point on that was that the agency would work a bit more to try to interdigitate these databases in a more fruitful way to get a better understanding of usage and diagnosis in all sort of settings; perhaps even use other databases, bring that into the discussion and analysis to get a better handle on what's happening between the zero to 17 year age range.

I think that FDA defines, in most cases, pediatric patients as less than 17. Others of us have different definitions of what pediatrics is.

In fact, wearing my AAP hat, the AAP talks about pediatrics up through the age of 26. So we consider neonates, children, adolescents, and young adults as a continuum of development and they're all very important areas.

I would ask whether or not the agency might, when they look at those data again, perhaps extend the distribution up through age 25, looking particularly at the age of 17 to 25 for a number of reasons. I think this presents us with a unique opportunity. I think looking at things from a broader public policy perspective and considering question number one for discussion tomorrow about the use, misuse, abuse, addiction, overdose and deaths in the pediatric population, that's a very important segment of the population.

We have some good basic science information that really sort of confirms our clinical impression that at least in males, brain development continues at least until age 25. And also we have a huge problem with the age 17 to 25 becoming exposed to these medications, becoming

addicted, suffering overdose and deaths, and delivering babies who have NAS.

I would say that this would be, if you can, a simple add on to whatever refinements you make in the data analysis that may shed light for us in terms of not PK safety, efficacy, because I think that's been done in the adult arena, but in terms of some of these public policy issues that can inform that discussion. So thank you.

DR. BROWN: Thank you.

Now we'd like to move ahead with our guest speakers. And our first guest speaker will be Dr. Charles Berde from the Children's Hospital of Boston.

Presentation - Charles Berde

DR. BERDE: Thanks very much for inviting me. I will apologize in advance for a whirlwind coverage of some of these topics, but was asked to give kind of a broad sense of the scope of how analgesics are used in children, a little bit about the state of knowledge, and we'll try to focus on some of the issues raised this morning.

I will talk very briefly about how one studies maturation of pain responses and analgesic actions; a little bit of the scope of prescribing for acute recurrent and chronic pain and palliative care; a very little bit about studies in the past and areas of knowledge; and about particularly the issue around risk-benefit considerations regarding opioids in the setting of chronic pain.

By background, I did an MD and PhD, residencies in pediatrics and anesthesiology, fellowship in pediatric anesthesiology, and I've stayed at Boston Children's since then for 30 years, practicing in the fields shown there, pediatric anesthesia, critical care, palliative care, and pain management. And my focus now is predominately in pain management.

My research focus is on some clinical outcome studies, clinical trials, some pharmacology, some on treatments of pediatric chronic pain, including rehabilitative non-pharmacologic approach; have worked on developing infant animal models of pharmacology,

particularly regarding local anesthetics. And a current area of focus is on developing novel prolonged duration local anesthetics.

As you all know, most children fortunately are healthy and they experience pain from time to time. They have needle procedures. They have fractures. They have immunizations. But most children's lives are, in our society, comparatively healthy.

At the opposite extreme are those with those very bad diseases and very painful diseases, diseases for which pain is a daily part of their life, some with uncertain lifespans, those with osteogenesis imperfecta, those with epidermolysis bullosa, those with cancer. So there was a discussion of what's the boundary of pediatrics. Depending on your cutoff, about 15,000 children get a cancer diagnosis annually in the U.S. Again, depending on your border, about 2,000 die of it.

If you look at pediatric palliative care services, the number of kids referred with cancer is relatively steady. The number of kids with

neurologic diseases, metabolic diseases, and that range of conditions, is the number that is growing in referrals and where we have the least literature and track record around symptom management, and I'll come back to that point later.

Sickle cell disease is a problem worldwide. In fact, in most of the world people with it, the largest number of people overall with sickle cell disease are in Africa where death is common by age 5, 6, 7 because of access to treatment.

In the U.S., I just show pictures of the spectrum of pain symptoms: dactylitis, consequences of recurrent vassal occlusion, consequences in bone of as you get older a vascular necrosis. And if you look at the spines of young adults with sickle cell disease, they show the consequences of repeated areas of ischemia and infarction through life.

There are groups around the world studying the ontogeny of pain responses. There is considerable maturation during the third trimester of normal gestation. There is a lot on how the

circuitry occurs in general. Behavioral responses are less localized. The infant animal and infant human withdraws with a lower threshold, meaning it takes a milder stimulus to get a reaction from the youngest of infants.

We know something about the facial expression and limb posture. We know quite a bit about kids in the past getting major surgery with inadequate or light anesthesia having profound hormonal and metabolic responses and autonomic responses.

That line of research has shifted more towards looking at the brain. So whereas in an era of Sunny Anand's early work, it was looking at heart rate, blood pressure, stress responses, many of the groups in the world focusing on that now are looking at what are the non-invasively measured brain responses to something like a heel stick, whether it's evoked potentials, features of the process or natural EEG, or FMRI.

Just to give you a sense, cortical responses that are specific to noxious events can be

identified by 28 to 30 weeks in infants in the NICU. Earlier than that, it is harder to tease out differences from a generalized higher cortical response from a specific pain response.

In regard to analgesics, there are groups around the world studying the ontogeny of analgesic targets, so that there is a growing body of information on ontogeny of opioid receptors, on local anesthetic mechanisms, and sodium channel evolution on inflammatory mechanisms, on microglial responses in spinal cord and brain.

We know a little bit about it, but it doesn't translate in an animal model as well in terms of saying, can we predict when efficacy would occur. Showing that receptors are present doesn't say whether they are coupled, whether they're second messengers and affecters are working the same, and whether pathways are connected.

All of you here are well aware of with other drug classes how infant animal studies have been a basis for pointing us towards unforeseen risks. And so the example of general anesthetics and the

lessons from infant animal studies regarding neurotoxicity is really something that this agency has taken a lead role on.

In the area of analgesics, there are groups working on it, but there aren't as many, and they're not working in the level of detail that you would see with those working on general anesthetic toxicities.

So for example, there have been works around the world on chronic opioid exposures in infant animals with and without pain models and looking at neuro development. And you can in many of those models show neuro developmental sequelae.

The infant rat has been the most used model that way. Infant rat, rats have great differences from humans in the time course of development, the critical periods, the time course of neurogenesis and all. Nevertheless, they are a convenient model.

For those not in the field, the first week of an infant rat's life in many ways roughly parallels prematurity in a human, meaning from

roughly 26 weeks to term are the first 7 days of a rat's life. So without creating an infant rat intensive care unit, one can study aspects of behavioral responses in a rat that's breathing on their own and that sort of thing.

For a lot of reasons, models of inflammatory pain, surgical pain, nerve injury, have been created in the infant rat, and correspondingly, models of analgesia have been created.

I want to explore a little of that with the four classes of analgesics that have had the most study in that regard, as shown here. Very little of medications for neuropathic pain.

About 45 or so years ago, acetaminophen replaced aspirin as the most commonly prescribed routine analgesic in pediatrics. Unless others in the room can tell me otherwise, we don't know its mechanism. There are still the range of candidate mechanisms. There's a range of disproven or lower likelihood mechanisms, but there's still controversy.

There is now PK and some safety data at all

ages. Previously there were no positive pain efficacy trials in young infants. There were fever trials and there were negative efficacy trials. There's now positive trial in the Netherlands in post-op pain in infants.

The side effect profile is low. There are some residual controversies about effects in asthma and about antagonism by 5HT-3 antagonists; in fact, the commonest acquired cause of hepatic failure in pediatrics from overdose. But overall, it has a good safety track record. It is prescribed. We know how to use it.

We know how to study morphine and other opioids sparing with it. So there was discussion this morning about opioid sparing as a paradigm for studying a test analgesic, and many groups around the world have used that paradigm to study acetaminophen, non-steroidals and other drugs.

This is just one among many of such studies showing a dose response. So in a cohort of kids having ambulatory surgery, intra-op management under general anesthesia -- this is from

Finland -- looking at percentage of children who did not need morphine in the recovery room versus a rectal acetaminophen dose, they showed a dose response.

It was mentioned in the morning that a group of us wrote a paper on opioid sparing paradigms published in Pediatrics a number of years ago. We followed that up more recently with a systematic review of all the trials we could find using opioid sparing to do an analgesic trial in children, and it's going to be discussed more by a subsequent speaker; but starting with about 5,000 abstracts and came down to a few hundred that were well-analyzable, and about 85 for which we could do quantitative meta-analysis to show that it is a practical and usable approach to analgesic trials.

This is from the study eventually published in JAMA showing IV acetaminophen in a blinded paradigm against placebo with morphine rescue in post-operative infants over a range of ages, but could show a morphine sparing effect in a blinded paradigm.

Non-steroidals have been studied in similar ways in over 300 post-op type trials. There has been demonstration of efficacy relative to placebo, effectiveness of a range of non-steroidals by oral, rectal, and intravenous routes. If you look in those kind of paradigms, in general pain scores are slightly lower, and they reduce opioid requirements by 30 to 40 percent.

The dosing per this morning's discussion is guided by adult dosing and PK. When one says what is a stronger non-steroidal, we know very little about what stronger means, does it mean ratio to equitoxic or recommended dose? But in the doses given in those trials, you can demonstrate a similar range of opioid sparing in a large number of them.

There's safety data on non-steroidals going back many years, so going back to the epidemiologic studies, pediatric office-based practice of kids getting short-term non-steroidal or acetaminophen in the office.

Safety data of a certain sort, safety data

meaning not clinically evident severe effects. My nephrologist colleague will say, but we don't know anything about a long-term course of if you take non-steroidal for a week, or 3 weeks, or 6 months, or through football season, what will be the lifetime effects on hypertension, nephropathy, gastropathy, and things. We know something about it from arthritis populations in the past, but relatively little with prolonged dosing.

I'm not aware of a true efficacy study in the immediate newborn period that has been positive for non-steroidal for analgesia. There's years past ones for heel stick and post-circumcision pain that were negative. I'm not aware of a positive trial in the immediate newborn period.

There's been this ongoing controversy regarding use for tonsillectomy, and there's been kind of a pendulum shift back and forth. So there was an era where many otolaryngologists avoided them because of bleeding concerns. The subsequent meta-analyses have been relatively reassuring about them. And more often, otolaryngologists are

becoming concerned about opioids and giving them again. And that's been a trend at major pediatric centers really around the U.S. as far as I'm aware.

There's the controversy regarding bone forming and orthopedic surgeries. There have been two meta-analyses and very little pediatric information. Even with the adult information, it's quite controversial.

Local anesthetics are widely used in children. They're used topically, mucocele. They're used for infiltration for procedures, and increasingly used for surgical pain, for regional anesthesia, for wound infiltration, and is a growing use nationwide and worldwide in pediatrics.

There is a body of PK data, and it comes from a range of studies, so that each of the amino amides widely used have the same trend. A question had been asked about general trends with drug classes. With the amides, the trend is similar that the younger infants clear amides more slowly so that bupivacaine with a terminal elimination half-life of around 4 hours in an adult can be, in

Miyazawa's [ph] study, 8 to 12 hours in the neonate and the youngest of infants. Chloroprocaine and esters cleared rapidly. The safety track record of topical local anesthetics has been good.

There is a multi-center consortium looking at safety of regional anesthesia in pediatrics. It is a partnership of a great number of pediatric centers in North America. They have a better sampling of major adverse events, less sampling of efficacy and positive outcome parameters. And the safety track record of that prospective database has been good.

I'll say that there is an example where infant animal surrogate models, much like with general anesthetics and opioids, we decided it was important to make an infant animal model for both peripheral nerve blockade and spinal local anesthetics. And have shown that at least several of the agents had a relatively reassuring profile in those settings.

How are local anesthetics used? They're used for wound infiltration during surgery.

They're used increasingly for peripheral and plexus blocks, and for epidural analgesia. If you look at trends over time, both in North America and Europe, the larger trend is greater growth in peripheral blockade and plexus blockade compared to epidural analgesia.

It is one of those situations where a technology has mattered to it. The development of ultrasound guidance I think has really dramatically changed people's willingness and success rates in doing these types of techniques. So that for thoracotomies in infants, it is increasingly something where paravertebral blockade is becoming widely used for pain after major thoracotomies.

In adult post-operative pain, there has been this trend for analgesic approaches that optimize analgesia while sparing opioids. And Henrik Kehlet and others were advocates of that in adults. There is an increasing body of publications on that approach for children as well, on using wound infiltration, regional anesthesia.

There's a series of studies looking at

round-the-clock acetaminophen and a non-steroidal with opioid as rescue. And there was a recent publication by a group in Denmark, which showed for a range of outpatient surgeries and very good scoring of pain after and scoring of analgesic use, that this kind of paradigm, including dispensing sort of a going home kit to the parents, led to a good set of outcomes.

The basic question, what is the evidence that you can safely combine acetaminophen and non-steroidals, and do you get additive benefit? And there's a systematic review I point to there arguing that there is a rationale to do so in post-op patients. And at least three studies I could find in children showing at least additive benefit with the combination in a post-op model with opioid sparing.

So turning now to opioids, which is the main topic of the meeting, they do have essential uses in pediatrics. They have uses for cancer pain, both disease-related, particularly mucositis, and tumor-related. They have essential uses for

life-limiting illnesses and end-of-life care for pain and for dyspnea. They have a role for post-operative pain. They have an essential role for sickle cell episodes. They have an essential role for critical illness and mechanical ventilation.

The discussion about trends in opioid pharmacokinetics. Of the opioids that have been studied over wide ranges, including morphine, fentanyl, sufentanil, remifentanil, the trend has been -- and methadone more recently -- that with different enzyme systems involved and different age groups studied, nevertheless the trend of slower clearance in the younger of infants has been a general trend for each of those except remifentanil.

Morphine has the largest body of data. Work from Ann Lynn and colleagues, Beasley and colleagues, Bray, Gitticor [ph], and many groups, took morphine infusion rates, took pharmacokinetics, and took what was a clinically titrated infusion rate, and came up with a kind of

age scaling many years ago that I show here.

There's a lot imperfect about that. If you look at the, quote, "effective infusion rates," or the blood concentrations at what were judged to be effective, they range incredibly widely. It's very hard to show a tight range on minimal effective infusion rate or concentration.

If you look at efficacy and safety, the trouble with many of those studies is they're mixed populations. So a population of post-op infants, when you dig deep into it, some of the kids were extubated and some of them remain intubated. And so deciding what is effective for a kid with an intratracheal tube versus extubated is challenging.

It's remarkably hard to -- regarding the question of can you define a minimal dose which is uniformly safe, if you ask is there an infusion rate of morphine or fentanyl in a post-op neonate that allows them to breathe on their own and have no incidence of apnea, you can't find such a paper. You can find ones where they report rates of apnea, but not either a plasma concentration or an

infusion rate with a below some tolerance rate of apnea.

A very basic question, ambulatory surgery is increasing everywhere, and if you look nationally at what age a kid can go home after surgery, it varies all over the map. And if you ask who goes home after getting opioids or with a dose of opioid, we did a survey of many pediatric centers, and the standards of 10 different pediatric centers vary widely.

I don't know of a data set of the rate of events of kids coming in. We tried from our emergency room and surgical records and all over a five-year period, and could say that essentially one kid had a spluttering, coughing, something-turned-blue, got-better event. But how that translates into for real life-threatening events at home, we have really very little information about.

I don't have to tell this group about codeine, other than its use seems to be dropping, and certainly in many institutions its use has

dropped.

So then, when would one use opioids, aside from post-operatively in pediatrics? Just very briefly, what's the scope of chronic and recurrent pain in children? If you look at adults, adults have commonly back pain, neck pain, headache, and many of them have it daily. Many people have, in my age range, have daily hip pain, knee pain.

The scope in children is radically different, so that children epidemiologically, 5, 7, 10, 15 percent of kids in school populations have episodic headache, chest pain, abdominal pain, limb pains. There are parsimonious algorithms for how to figure out who has an underlying disease and who has a benign situation. The issue is getting people to stay in school, and many kids miss a few days of school, enough that 20 percent of school days missed in the U.S. is for headache and abdominal pain, but most kids just miss school now and then, not regularly.

Then there's evidence that if you're a community pediatrician, most of your treatment of

those kind of things is not with medications but it is with advice and counselling and guidance and lifestyle change and exercise and cognitive behavioral therapy. And there's a very circumscribed rule for analgesics for those.

Who comes to pediatric specialty centers? Rheumatologists, neurologists, pain physicians, and others, it's kids with inflammatory or neuropathic diseases. Neuropathic pain in pediatrics has a different epidemiology than adults, different causes, but those are people seen in pediatric pain clinics.

Complex regional pain syndrome is something that it happens rarely before age 6, 8, 10, goes up in instance a lot around age 10 to 12. One thousand three hundred kids with that have come to our clinic over the last 30 years, and we've studied it over that time period.

It's something that has a remarkable pattern that overwhelmingly you can make them better with a regimen of physical therapy and cognitive behavioral therapy. And there is a model of it

involving structural and functional changes in brain circuitry involved in pain that is shared with other kinds of persistent pain, as shown here. So overwhelmingly the treatment of this very miserable kind of pain, in our view, is not with opioids, but rather with those kinds of treatment.

In adults, there are a number of medications that have been approved and have some evidence for efficacy for neuropathic pain. They're not magical. They have side effects. They have only partial efficacy. There is very little, even in case series, on those in children.

Dr. Weissman, one of our speakers, has written a case series in one context, others, but they're mostly case series. We prescribe them based on extrapolation from adults. We know about those medications because of trials for epilepsy and mood in children. There's PK, there's safety, but very little regarding efficacy.

There is the literature on opioids for children with advanced cancer, and it's a literature that goes back to Angela Miser and

colleagues in the 1980s, and from centers around the world, indicating that opioids provide analgesia with good effectiveness, with side effects that can be managed in most cases; that they can be given by a range of routes; that many kids need switching and titration and adjustment, but that they have a real role for those kids.

Again, advanced cancer and end-of-life care for cancer, no more than about 2,000 kids a year in the United States.

For those of you who don't know it, there's some important age-dependent biology that if you look either in humans or in animals, the younger you are, the more rapidly you develop tolerance to opioids. And this phenomenon, opioid-induced hyperalgesia, seems to be a real clinical effect, that in some people, certainly in the animal, and in some people a change in pain responsiveness occurs with chronic dosing.

We know very little about its frequency in pediatrics. We know very little about how you distinguish it clinically from tolerance or

increased pain stimulus. But at least in the animal, it is clear that the younger you are the faster it develops.

I think where we see this age dependence most is in critical care where 70-year-olds in an ICU escalate opioids slowly, 30-year-olds faster, neonates become profoundly tolerant to opioids.

We looked at it many years ago in a cohort of kids with cancer, showed a subset of kids with more than 100-fold escalation of opioid dosing, to a range of like adults getting more than 100 milligrams of IV morphine an hour, and some getting thousands per hour, and becoming profoundly resistant.

The controversy around opioids in adults, I am convinced by the evidence that at least for chronic low back pain, non-specific chronic low back pain in adults, there is a lack of long-term benefit as a whole. There are individual patients and all, but where it has been studied, it is very hard to show impact on function or disability. I think those concerns are shared for children by

concerns about effects on mood, cognition, endocrine development, and this phenomenon of tolerance.

The problem is the grey zones. And those of us who do management of chronic pain and palliative care, there's this whole set of diseases in pediatrics of uncertain prognosis, or prognosis that's shifted.

This is the chest radiograph of a patient who I admitted as a pediatric resident in the 1980s. When I was an intern in 1980, median age of death was 19, and she died in her 50s. And now median longevity at good centers is 40 or more, likely to be longer.

So when thinking about the trade-offs, and other speakers are going to talk about trade-offs, we have a great number of diseases. There are many rare diseases, but there's a lot of them in any pediatric center, and patients who have problems that are painful, but may be so for many, many years.

A patient who had Ewing sarcoma and a

hemipelvectomy at age 3, who's tumor-free, has an expected longevity that's quite long, and you don't have to be a radiologist to notice that there's no hemipelvis over here, and she has had pain ever since she could talk about it.

This is kind of a whirlwind scope of some of the ways that analgesics have been studied, that opioids are used, and some of the trade-offs. I think the general conclusions are, there are differences from adults in the ontogeny of pain circuitry and analgesic responses, certainly in PK and safety issues.

There are differences in who has chronic pain and what their trajectory is, and what your goals are in treating chronic pain. We have evidence for safe prescribing of many analgesics, and extrapolated evidence for many of the opioids. And to echo many of the other speakers, we do need trials to understand better how to prescribe all analgesics, but in particular opioids safely for children with acute pain, chronic pain, and in palliative care. Thanks.

DR. BROWN: Thank you, Dr. Berde. That was an excellent presentation.

We want to continue with our next speaker, Dr. Harold van Bosse, who will be giving a presentation. And he represents the Pediatric Orthopedic Society of North America.

Dr. van Bosse, welcome.

Presentation - Harold van Bosse

DR. VAN BOSSE: Thank you very much. I want to thank the advisory committees for inviting us to speak, or inviting me to speak, as a representative of the Pediatric Orthopedic Society of America, and also for the American Academy of Orthopedic Surgeons. I am an orthopedist for children at the Shriners Hospital for Children in Philadelphia.

Orthopedic surgery treats a number of different body areas, the upper extremities, the lower extremities, the spine. And we treat conditions related to trauma, to deformity, either those that are congenital or acquired. For example, I have two niche diagnoses I'd like to treat. One is arthrogryposis. These are

congenital deformities. I also like to treat patients with Prader-Willi syndrome who have acquired spine deformities over time. I also treat tumors and syndromes, such as cerebral palsy.

Pain is inherent to our specialty. As you know, as Dr. Berde discussed a number of orthopedic issues, patients present with pain, such as fractures or injuries, something along this line, or they have infections that they present with, or tumors.

Also on the other side of it, we create pain. Patients who have corrective surgeries will oftentimes go through pain. So if you take this patient to make him into that, there's a lot of discomfort involved with that. There are relatively few chronically painful conditions in pediatric orthopedics, but there are a few.

Pain management is very important to us, and we realize that patients have a very keen awareness of pain. And on top of that, they have great anxiety related to pain. So once they start thinking that we're going to cause them pain from

experience, then the pain response becomes more and more amplified.

They don't always understand why they're being subjected to pain, and we know this in our very young children that we treat. The older ones, it's easier because they understand what you're trying to do for them.

There's also becoming more and more of an understanding that there's a post-traumatic stress disorder that comes either from children who have been injured, or children who have undergone treatments that are painful. And when you have children who require repeated procedures, this becomes more and more difficult.

In the pain management, those are even discussed, but we have different options that we use, our anti-inflammatory medications, analgesics, excuse the spelling there, and of course the opioids. Disadvantages of the opioid medications that we're all familiar with, of course the respiratory depression, gastrointestinal dysfunction, nausea, itching, confusion,

habituation or dependence, and of course the abuse potential.

In preparation for this presentation, we created a survey for the Pediatric Orthopedic Society of North America asking members for their practice habits. We got about a 25 percent response rate.

Just real quickly, we have a society that is becoming big quite quickly. So here we have, we see that 68 percent, almost 70 percent of the respondents, were people with over 10 years of experience. What that actually tells us is that even though we only had 25 percent membership responding, a lot of those were older members who had a lot more experience. So hopefully this will make this all more relevant.

Our first question was, who directs your pain management? And so the orthopedists said this, 75 percent of the time they did it. They would turn it over to a pain specialist, either a pediatrician, a pain physician of some sort, a nurse practitioner, an anesthesiologist only 3

percent of the time. But 22 percent of the time, there was a combination of work.

What most of the comments were is that in-house, especially in the intensive care unit, the pain management would be left to somebody else, and then at discharge, it would be left to the orthopedist.

We wanted to talk about different specific indications that we have where we create pain and how those are treated by different practitioners, just to get an idea of what the practices are. So one of the things we treat are club feet. This is done with serial casting. Every week the patient comes in, we put a cast on them. And when the foot is then corrected by that, the last thing that we have to do is take care of the Achilles contracture.

This is done oftentimes in a clinic, sometimes in the operating room, with a percutaneous Achilles tenotomy. Just take a scalpel, cut through the Achilles, and altogether put in a cast that heals up over a period of weeks,

and they do very well.

So we asked what do people give for opioid analgesics after that? Eighty-six percent of respondents said they gave nothing, 6 percent said hydrocodone of some sort, and just about 4 percent said acetaminophen with codeine. They're not applicable to those that did not do this procedure. And if anybody gave opioids, it's for a week or less time.

Moving up slightly, outpatient fracture reduction. So if you have a fracture like this, in the emergency room, we make it straight, put it in a cast, and then send the patient out. And what we found is that about a third of the respondents said they gave no narcotics. Forty-six percent said that they would give a hydrocodone type narcotic. Oxycodone would be 14 percent, and acetaminophen with codeine would be about 20 percent. And there's a smattering of other things.

If you look here, you'll see that the percentages don't add up, and that's because the people who answer positively to giving opioids

sometimes would give one or a different one, depending upon what they thought the patient needed, so the percentages actually come out over 100 percent.

How long would people give the analgesic? Most of them gave for a week or less, although some would give it for a little bit more than a week. But ibuprofen is the main alternative that was given. And one of the comments that we saw pretty much from here and all through all the different procedures we're going to talk about, is a number of people would say that they would only give instantaneous release oxycodone and not give OxyContin, the extended release.

When we went back to try to get some clarity on that, some of them said it was because of speed of onset, that if they felt that their patient who was uncomfortable, they wanted to give something right away, so it's seen more as a PRN medication. Other ones said that it was actually due to state pressure in the region where they practiced, that there was a great attention given to opioid deaths,

and they wanted to make sure that they were not in any way contributing.

What about a simple operative fracture? You have an elbow fracture, supracondylar humerus fracture, that we do a closed reduction, so we don't open the skin and put some pins across it. What would people do for that? No narcotics in about 10 percent or so. Then we have hydrocodone was probably the most commonly prescribed. And then it would be the oxycodone type medications and acetaminophen again with codeine about 21 percent. And there's a smattering of other medications that were given as well. How long would these medications be given? Usually a week or less, but again, there's a few people that prescribe it for more than a week.

In the arthroscopy, this is where you infiltrate the knee with a fluid, and then place a small camera type device in through a small portal in the skin, and then other portals are used for actually manipulating things inside the knee, and it's done usually as an outpatient procedure.

Here what we find is that no narcotics were given in about 6 percent of practitioners. Again, hydrocodone was the most popular one prescribed; oxycodone second most, but at a much smaller amount; and acetaminophen and codeine was again prescribed but at a much smaller amount as well.

Here the medication usually given for a week or less, but about 10 percent of practitioners would prescribe it for more than a week.

Then moving up to hip procedures, here's a child with a dislocated hip that underwent reconstruction of that hip. And these oftentimes are big exposures, and they're in a cast for a period of time.

Four percent of practitioners said that they did not give narcotics as an outpatient. Hydrocodone again was the most commonly prescribed, and then oxycodone was about 30 percent of prescriptions. And again, acetaminophen with codeine came in at about 16 percent, and there's a smattering of other ones that were given as well.

In a larger patient, or an older patient,

again hip procedures. These can be very big reconstructive procedures. So here's something, a hip that looks like that, an unstable hip where you try to get it better covered. Again, these can be large exposures of big bones.

Here, no narcotics in 5 percent of the patients -- or of the prescribing physicians. Hydrocodone 62 percent of the time, oxycodone about 30 percent of the time, and acetaminophen with codeine still hanging on about 14 percent.

Here the medications would be given a week or less in about 50 percent, but you'd have about 35 percent that give it for up to 2 weeks, and even some that would give it for going up to about 4 weeks.

Spine fusion, where we have a spine deformity, a large incision, in many cases the entire length of the thoracic and lumbar spine to get them straightened out. Here, no narcotics 1 percent of the time, but otherwise, it's a fairly equal mix of either hydrocodone or oxycodone. Acetaminophen with codeine a much lesser amount,

and some of these other medications, even though still small numbers, but they become more important here, the oral morphine and the hydromorphone.

Then for the length of time that these were prescribed, a week or less happened only in a few of the patients. One to two weeks was more common. Four weeks still was more than a quarter of the patients. And one of the things that's important here is that movement is very important early on. We want to control the pain so we get these patients up and moving, because they longer they're at bed rest, the greater the risk they are for respiratory issues, for an ongoing ileus. So we want to get them up and moving quickly.

We also want to get them under oral pain medications quickly so we can get them off the IVs. And we're also trying to do whatever we can to get them comfortable enough to return to their normal routine, such as getting back to school.

We had a question about, what about narcotics as a backup plan? There's a number of states that no longer allow phone-in prescriptions

of narcotics, that they will only take a paper prescription. So what we asked is, well, are there situations where you would give a patient a paper prescription for a narcotic, even though you're not sure if they're going to need it, if they need to fill it or not? So we called it kind of a prophylactic narcotic prescription.

Fifty-eight percent of our respondents said that they would do that. The comments were that a lot of my colleagues work in areas where either they're in a rural area where people travel great distances to come to them, or they're in a referral center where, again, people travel great distances to come to them.

So if they do not have adequate pain coverage, and they need to have something, they cannot be expected to travel that distance back to the hospital to get a paper prescription. And furthermore, a lot of my colleagues work in places where weekend coverage can be difficult.

So again, if somebody needs a pain prescription over the weekend, they might have to

tough it out until Monday before they can get their pain treated. So in that case, those practitioners would rather give them a prescription that they can take with them and fill. That means there's a lot of unfilled prescriptions out there.

What about giving opioid narcotics to pre- or non-surgical patients, such as those that don't have a fracture or are waiting for their surgery, but haven't had it yet? Here we only had about 15 percent of my colleagues would give any sort of a prescription to those patients. Most of them said that they'd rather stay with the things such as the anti-inflammatories to work them through.

But the most common place where such a prescription was given is for a diagnosis such as this osteoid osteoma, and Dr. Berde mentioned that. These are children with a fragile bone disease, and they oftentimes will get fractures, and it happens in the most inopportune moment. So having a narcotic on hand is very helpful for these patients to be able to tolerate their condition.

We asked a question about what are my

colleagues' experiences with opioid abuse in pediatric patients? And 21 percent said that they knew of an occasion where that had happened; 79 percent said they didn't really have any experience with this. And most of the time the thought was that it happened with patients who had chronic pain conditions, who had gotten to the point that they just become habituated on their medication and then addicted to it.

Also, there were some comments about knowledge of patients actually selling their pills. And some of the colleagues, even though saying that they did not know of a case where it happened, they had their unconfirmed suspicions.

What about abuse by patients' family members? And here it was a little more concerning. Thirty-nine percent said that they knew of at least one case. Now mind you, it doesn't mean that 39 percent of the time this happens, that means that 39 percent of my colleagues knew of an event that this happened during their career. And some estimate that it was about half a percent of all

patients had this issue. Again, many unconfirmed suspicions, and particularly red flags went up when patient families requested refills of medications, and occasionally a fictitious pain would be identified in a patient.

In conclusion, to pull this all together, outpatient opioids are extremely important in pediatric orthopedics. We use them widely. We try to decrease hospital stays. And as many of you are aware, there's more and more pressure placed on us to discharge our patients sooner from the hospital. And many of the procedures in the beginning of my career that were one or two nights overnight stay are now seen as outpatient procedures.

Oxycodone, either in the immediate-release form or in terms of OxyContin, was used in about 14 to 30 percent by my colleagues as their primary outpatient opioid; mostly used in the more painful procedures, such as the spine procedures.

If I can back up a second, OxyContin probably is used more often in say spine procedures than the oxycodone because here you know that

there's going to be ongoing pain. So if you can give them medication that lasts for a significant period of time, then hopefully they do not take it on an episodic basis, but will take it on a routine basis and require less pain management all together.

One of the comments made is that these medications should be trialed with the patient in the hospital for a day or two prior to discharge to make sure that they're working appropriately.

Length of use, in most cases the opioids are used for less than one week. But some extreme situations, some of our bigger procedures, they can be used up to four weeks. But the medications should be refilled only rarely, is what most of my colleagues felt.

Then there's the concern about the prophylactic prescribing, or the prophylactic provision of opioid prescriptions, and that we still need to figure that out better, how we can work with the states to try to do things to lessen the risk of abuse, but also make sure that our

patients are well-cared for and that they don't go an extended period of time without medications if needed.

The potential for abuse is well recognized, and we're ever vigilant, and we're very concerned. One of the things that we like to see happen are programs for teaching parents before they go home how to appropriately use the medications, what warning signs to look out for if they think that their children are becoming addicted, such as signs of sedation, nausea, or dizziness. And make sure that only the parent is the one who dispenses the medication, that the child is not give free use of the medication. And possibly also to use journals to keep track of how often the medications are used.

We certainly think, as you all know, more research is necessary to come up with better pain strategies to manage these patients. Thank you very much.

Clarifying Questions

DR. BROWN: Thank you, Dr. van Bosse.

We're going to take clarifying questions to these speakers, Dr. van Bosse and Dr. Berde. At this point, are there any clarifying questions? Dr. Higgins?

DR. HIGGINS: I really appreciated the survey that van Bosse presented, and I have a couple of questions. As you know, a gerontologist, I'm really focused on age and aging issues. I'm wondering, you mentioned that some of the demographics of your survey participants were on the older side, or that's at least what I took from your mention of that.

I'm wondering how prescribing differences made -- or be presented by age. I notice that there were a lot of no narcotics used for some of the really invasive procedures, which I found striking.

DR. VAN BOSSE: Certainly, one of the issues is what form the medicine is given. So we use a lot of elixirs for the younger children, and of course pills for the older children. Elixirs are nice because you have a lot better ability to

tailor how big of a dose you're giving. When you're left with pills, it's one big bulk at a time.

You're right. I was struck also by seeing that, for example, spine procedures are done without needing narcotics afterwards. And then you're left wondering, are there really heartless colleagues out there, or are there people who have a might better idea of how to manage the pain that I don't know yet. So I think it's going to behoove us to look more at our membership and get more input on what people do for pain.

DR. BERDE: Just a question. Do you think a few of those with spines were people with either high myelomeningocele and neurologic disabilities or conditions where the pain, either they thought they were deafferented, or pain was hard to assess?

DR. VAN BOSSE: Well, you could be right, but we were asking colleagues what they did in their practice. So yes, so even somebody who does a lot of spine procedures, they might have some myelomeningocele kids, but then also a lot of

intact kids.

DR. BROWN: Dr. Patrick?

DR. PATRICK: Hi. Stephen Patrick from Vanderbilt. The last few speakers spoke a bit about abuse potential and some concern from that. I was curious, I haven't heard anyone mention yet prescription drug monitoring programs. And I wonder in the survey data or the like, the prevalence of use of PDMPs prior to prescribing and also for use of referral to treatment for substance use disorder.

DR. VAN BOSSE: We didn't query on that, and I didn't get much back in the comments on that. For most of us, I think these are very new programs. In Pennsylvania, in fact, I've just been asked to register for such a program, so I don't think we have a whole lot to look at yet.

In terms of programs for those that are addicted, there were a couple of comments on that in terms of getting those patients back to a pain specialist to get that taken care of. So we don't do much as orthopedists in taking care of those

problems. We only create them I guess.

DR. BERDE: Similarly, Massachusetts has just broadened the use of prescription monitoring program. In our hospital, all prescribing is electronic. And we went to a system of, through the pharmacy, tracking everyone who gets multiple opioid scripts, tracking features of, and having an automated notification to physicians internally if a patient has gotten repeated scripts or gotten the from others.

That's done at the level of the informatics and hospital pharmacy people. We are gathering data on outcome of that. We have the good fortune of having a very active substance abuse program. Your subsequent speaker, who will talk more about that.

DR. BROWN: But, Chuck, that's only within the Children's Hospital that you're doing that evaluation, or is that tied into --

DR. BERDE: It's tied. So the pharmacist tied to the database that goes outside as well. So that if a patients getting multiple scripts from

providers inside and outside, there is a look into the system for that. But within, it's automated by the prescriber -- in other words, if you're getting multiple scripts, it triggers a pharmacist to go looking further about it, outside as well as inside.

DR. BROWN: Dr. Hoehn?

DR. HOEHN: I had a question for Dr. van Bosse. I wondered, in some of the patients that were not having narcotics after spines, if you thought there was an increased use of Toradol in those patients. And I also didn't know if you and any of the groups of orthopedic surgeons were doing any safety trials or anything looking at the bleeding risks or any of the reasons that people don't use other non-steroidals post-op.

DR. VAN BOSSE: To answer the second question first, I'm not aware of any of those trials. And then getting back to the other medications, so Toradol was mentioned by a number of respondents, as was gabapentin. So there was more attempts to try to go to that.

One of the problems with Toradol, very much to what Dr. Berde spoke about, is we have concerns what the anti-inflammatories do towards bone formation. So when we do procedures such a spine fusion, you're trying to get bone to heal to bone.

The same thing with one of the procedures that we do that cause chronic pain is bone lengthening, where you put an external fixator on a bone, you cut the bone, and then gradually over time you're stretching that bone out over a series of weeks. And that can cause ongoing pain. And that would seem to be the optimal place to use an anti-inflammatory, but if it slows bone healing, then it can really be a problem.

DR. BROWN: Dr. Walco?

DR. WALCO: I guess there's an issue that came up as I was listening that I reacted to a little bit. And that is, I'm looking at the questions that we're going to be discussing and we're using this as background material. And one of the challenges, I think, it's not explicitly stated here, but certainly something we've

discussed is, what a drug is labeled for versus how a drug is used. And the FDA's job is to label drugs, and I'm not sure there's all that much control over how it was used.

What we just heard in the orthopedic presentation was that OxyContin is used instead of oxycodone because these adolescents who have spine surgery are going to be in pain pretty much around the clock. So use the drug that's sustained release, and that way you end up using less of it.

Well number one, I'm not sure there are data to show that you use less of it. And number two, that's definitely not the way oxycodone was labeled. I'm sorry, OxyContin, thank you, was labeled. And that's what sort of got this whole ball rolling. OxyContin is to be used for very specific conditions where the patient is opioid tolerant and has shown the demand for that drug around the clock.

I juxtapose that with what I heard we really want to be aggressive with these drugs because we want these people to be up and moving. Well, then

that would say to me that the pain's not necessarily a steady state, but it's more associated with activity.

So I think -- and please, don't hear this as a criticism of you or your talk, because I don't intend it that way. You presented the data as people prescribe it. But I think that this is something that we are going to need to grapple with in some form or another, unfortunately, in these discussions.

DR. VAN BOSSE: So let me see if I can take the part about OxyContin spine surgery first. I suppose the way to look at it is if you have somebody that you're trying to move several times a day in the hospital environment, or when they go home, we don't want them to be sedentary, we want them moving around, you don't want to end up in a paradigm where, oh, I'm going to move you in 10 minutes, here's your medication; or I want you to move now, oh you can't, you're having too much pain.

If we can put them on something that gives

them a steady state of pain relief, it's easier to mobilize them that way. And then if they're having pain above that, then you can try your anti-inflammatory or something else to give a bump of pain relief.

DR. WALCO: So the question I would have, and I will frame it as a question, are there data to show that that's the case, or is that logically this is my reasoning, and so I'm going to proceed this way? Because I would say, from having dealt with these patients, they are in a fairly high steady state of pain that is round the clock, and it goes up significantly when they get up to use the bathroom or physical therapy, et cetera.

So I would sincerely doubt that the OxyContin is going to cover their pain when they have those episodes anyhow. And so if somebody could show data that clearly indicated that using an extended-release formula truly was effective and used less opioids, I'd be in your corner in a heartbeat. But I think it's done more on speculation and reasoning rather than actually

having the data to show it, unless you can steer me otherwise.

DR. VAN BOSSE: No, I think you're absolutely right, and I think that's one of the real problems -- I don't know if it's just my field, or if that is a number of fields -- where we do things because we think they work, not because we have any data to prove it. And is that because we're lazy looking for data, or is that that the data just isn't there, that no one has been able to do a study such as that?

So you do it more as anecdotal medicine, you know this seems like it's worked, and that's why we do it. And every institution seems to have its own ways of doing that. And then when it hits a point where you have enough excitement about it, then you write it up or you present at a meeting, and more people start doing the same thing.

But even in my institution, I've seen us go from, it's been OxyContin, now we're slowly moving over to Ultram. And again, I don't know what drove that, but that's kind of what we're starting to

prescribe more for our patients.

DR. BROWN: Dr. Havens?

DR. HAVENS: Thank you. A question for Dr. Berde. What a great talk. I think it was right on target. Thank you very much.

If we could bring up his last slide, you make the statement that acute and chronic pain in pediatrics has important differences from adults in epidemiology and biology. Now, is it your opinion therefore that these differences in biology are great enough to argue somewhat against perhaps using extrapolation studies like we've been talking about in the first part of this meeting?

DR. BERDE: Some of the differences in biology are response to injury. A classic example is brachial plexus avulsion in a motorcyclist causes neuropathic pain incredibly commonly. Brachial plexus injury in a newborn with difficult delivery, we -- where's Dr. McCann? Dr. McCann and I and others looked at a couple hundred kids with that, and it's rare to have pain after that, except in those who get nerve grafting.

You get shingles, if you're 70 you're going to have pain. If you're 20, you're unlikely to have pain. Many kinds of things have an age dependence of likelihood of chronic pain for those kind of comparisons. So that's what I meant in that kind of thing.

But in terms of everything we could find in terms of analgesic effects of opioids, non-steroidals, local anesthetics, and acetaminophen, we could not find in acute pain trials much evidence of a pharmacodynamic difference age 2 and up. If you tried to look at decrement in pain scores, or requirements scaled in a number of ways, or blood concentration at analgesia, there weren't important pharmacodynamic differences in those four classes that we could find. With local anesthetics, it's local dosing and local effect. The others were blood concentration and effect.

So if there is a great age-related difference, in those kinds of pharmacology we don't, but there are clear differences in who gets

different chronic pain conditions and who gets different patterns of injury, things like that. So that's what I meant.

Tolerance I do think is quite age dependent. Again, you go through NICUs, and the phenomenon of opioid tolerance is such a daily issue. If you look at bed utilization and kids getting discharged from NICUs and all that, you don't find 70-year-olds with COPD on them as much and being escalated as much, to be on a ventilator. And you could say maybe it's because whose kinder to who and who fights the ventilator and all that.

But even with cancer populations, if you look at rates of opioid escalation in the adult cancer world versus pediatric cancer, it seems faster in childhood. And I just think, like in the animal, you can create tolerance faster the younger you are.

Does that answer where you were going with that?

DR. HAVENS: Yes, it's very helpful. So the PK/PD relationship, I hear you saying, is

relatively constant or would allow extrapolation studies over age 2, perhaps not under age 2. But the disease processes themselves might be enough --

DR. BERDE: So are you asking me if you --

DR. HAVENS: I'm confused there because if the disease processes aren't similar or the response to stimuli are different by age, then extrapolation studies would be more difficult.

DR. BERDE: I think I understand you. If you take a flank incision in a 1-year-old or a flank incision in a 55-year-old, 1-year-olds seem to have pain for a shorter period of time. So there's many types of surgery with a fan and steel incision in a 3-year-old having ureteral implants versus a fan and steel incision for hysterectomy.

The time course of pain, even when you count in what is all of our expectations around it, does seem somewhat different. So there are aspects where recovery seems faster the younger you are. There are animal models, which give divergent results on that. And second surgeries, in the animal if you do a surgery very early in life, and

then do a repeat surgery in adulthood, you get markedly more sensitization than you do if you haven't had the first one.

So I think it is complicated. I think what you described as the post-traumatic status of -- the kids who've had multiple, multiple surgeries have both a fear and anticipation response, but I think they have a hyperalgesia too from early-life injury and recovery from that, at least by analogy to infant animal surgical models.

DR. BROWN: Thank you.

DR. HAVENS: Part of this comes from trying to anticipate the questions for tomorrow and trying to be responsive to the FDA's statements from earlier today about the difficulty of doing these studies directly. But many of the things you say argue, I think strongly, for direct studies in the affected populations in children and make it more difficult to be comfortable that extrapolation studies will be as helpful as we wish.

DR. BROWN: Dr. Lasky?

DR. LASKY: Thank you. I thought

Dr. van Bosse did a very good job of describing the use within the population of orthopedists, and I was wondering if we could put this in context with the presentation by Dr. Pham this morning.

I'm not sure if orthopedists would be considered to be part of the group of pediatricians or would be a another group in addition to the pediatricians. What I'm going for is to find out what percentage of the outpatient prescribing would be accounted for by the group of physicians you were describing.

DR. VAN BOSSE: Gosh, I think that one's out of my wheelhouse. I'm not sure how to answer that.

DR. LASKY: I realize it's probably the two of you have to get together to figure it out. You might not have it right now. But offhand, would you be considered a subset of pediatricians, or would that would be a separate specialty?

DR. VAN BOSSE: We would certainly be a pediatric subspecialty, and probably more under the rubric of pediatric surgery.

DR. LASKY: So it could be part of that

prescribing, or it could be separate from that prescribing.

DR. VAN BOSSE: My guess is that we were included in that prescribing, yes.

DR. LASKY: Okay, great. Thanks.

DR. BERDE: I think you're going to hear, now that hospitals are doing all electronic prescribing, from some of the hospitals around here, as outpatient prescribing, orthopedic prescribing, hematologists, oncologists, dentists in declining amount, at least a few places, are major groups for it.

Community pediatricians prescribe relatively few in the data sets that we have. So what's lumping in as pediatricians include oncologists, hematologists, orthopedic surgeons being a prominent group, general surgeons, some others. But there are now data from electronic prescribing, both inpatient and outpatient, from a number of hospital systems.

It's not national data the way that those are, but I think it would be important going

forward to take the kind of data that Dr. Pham did and link it to large pediatric centers and their EMR-based prescribing data. Just because I think in hospital and leaving the hospital are really -- in trying to understand important roles of opioids, and particularly all of that about who's getting long-term opioids in the first year of life, overwhelmingly it's kids who are survivors of critical illness, and you have to understand their inpatient course to know where you're at with that part.

DR. LASKY: So I agree with everything you said, but as you were speaking --

DR. BROWN: Just one second. Can I just ask Dr. Hertz for a clarification here about the panel asking our speakers about issues that will be up for discussion tomorrow? Is that reasonable or not?

DR. HERTZ: Yes, we really should be focusing on clarifying questions just so we can get through all presentations.

DR. BROWN: So this line of questioning that

we're following now should or should not be followed?

DR. HERTZ: Well, I think in terms of trying to understand if one of the talks is relating to another, seems clarifying to me.

DR. BROWN: Go forward.

DR. LASKY: Just to finish my question, just I wanted to understand what percentage of the prescribing that Dr. Pham presented would be accounted for by the picture portrayed by Dr. van Bosse. And if it can't be answered now, just to keep it in mind.

DR. BROWN: Dr. White?

DR. WHITE: Thank you. Boston Children's has a huge pediatric cardiovascular surgery program. Have you looked at median sternotomy in infants? It would be a great controlled group. You looked at thoracotomies, but median sternotomies occur on a regular basis in the cardiovascular surgery.

DR. BERDE: We have an ongoing project looking at their time course of -- so the whole

issue of weaning kids from opioids -- and many of you know there was a national multi-center study, the RESTORE study, around mechanical ventilation and sedation for that.

As a spinoff of it, there was developed by Martha Curley and others a set of algorithms for how to use withdrawal assessments as a criterion for not just the baby is fussy, let us slow down the wean, but let us wean in a criterion based way.

There's an ongoing project of which the cardiovascular program is a major participant in it. The data so far, it has resulted in shorter weans and fewer kids going home on opioids since initiation of that.

Because there have been critical incidents of kids weaning from -- kids with congenital heart disease, who don't tolerate mistakes well, and they go home, and the parent misdoses or whatever, and critical incidents have occurred because parents don't know milliliters, teaspoons, changing concentrations, et cetera. In response to that, there's been a very strong effort to get as many

kids as possible off of opioid before going home.

But your point about sternotomy, overwhelmingly, it is not sternotomy pain as much as duration of ventilation that sets the duration of opioid use. So if you take kids with ASDs, for example, their opioid use is quite short, and shorter for a sternotomy than an open lateral thoracotomy. Duration and amount of opioid use is based on the smaller subset who have critical illness, who have single ventricles, and a range of complications. Those are the ones on a lot of opiates. So pain is not the explanation of it.

DR. WHITE: I'm thinking in terms of age related use of the opioids. Because there's a significant difference between a newborn that gets a thoracotomy and a 12-year-old, in the pain that they experience.

DR. BERDE: There is, but there's also the difference in how sick they are to get the --

DR. WHITE: That's true.

DR. BERDE: Right. That is, if you have more than one ventricle and one outflow tract,

you're a healthy kid in that population.

DR. WHITE: Well some of them with one ventricle do pretty good.

DR. BERDE: Or they're transposed, right. But, yes.

DR. WHITE: Thank you.

DR. BERDE: Sure.

DR. BROWN: Dr. Staffa, I'm sorry, I didn't mean to cut you off, but you had a comment?

DR. STAFFA: This is Judy Staffa. I was just going to suggest that we'll look into the data to address Dr. Laskey's question.

DR. BROWN: Dr. Chai?

LCDR CHAI: I'm sorry. Please correct me if I'm misinterpreting your question. I was looking into the data.

So orthopedic surgeon does come up as a specialty in the table. If I can refer you to the background package, it does fall further down, which is why we didn't show it on the slide.

I would refer to page 23 of the addendum. That is when the prescriber self-attributes himself

as an orthopedic surgeon. So pediatric orthopedists actually makes up a very small proportion of what we grouped into the pediatric specialty category, but they are a very small proportion of that number.

DR. LASKY: Okay, so --

DR. BROWN: By the way, I don't believe we have that addendum. So do you think you can pull that up? We don't have that addendum.

DR. LASKY: So thank you for answering the question, what is the percentage? And is it a percentage of pediatricians or a percentage of outpatient use?

LCDR CHAI: So for example, for the -- let me read this exactly. The 2 to 6-year-old population for a number of prescriptions dispensed, pediatric orthopedist was about 1 percent.

DR. LASKY: Okay. That's really helpful. And in the next age group up?

LCDR CHAI: Sorry about that. So we divided our data by IR and ER as well.

DR. LASKY: Correct. Right.

LCDR CHAI: So this is of the ERs. I think I have to get back to you on all the specific ways we extracted this data.

DR. LASKY: Great. Thank you very much.

LCDR CHAI: But we did take a look, it's just they were so small that you would just get a huge line listing if we'd broke it out, that we wouldn't be able to fit it all into this review, which already has huge tables. But orthopedic surgery does show up in the 7 to 16 category in the table that is in the addendum PDF that was in the background package , on page 23.

DR. LASKY: Thanks very much.

DR. BROWN: Now that we have the data in front of us, could you just go over that again?

LCDR CHAI: Sure. If you scroll down further to the 7 to 16 age group, it is its own subspecialty. I'm referring to that line under the extended release, long-acting opioids, under the 7 to 16. And there was more prescribing captured for that type of prescriber than for pediatric surgery, is the way it was termed. But these are

all of course outpatient data, which is why it may not be fully representative of everything.

Right there, sorry. And for IRs, it's right here.

DR. BROWN: Any other clarifying questions before we have a break and come back for some more of our invited speakers? And as I said, we will have an opportunity after the remainder of our speakers to ask questions.

(No response.)

DR. BROWN: If there are not any other questions at this point, why don't we take about a 15 minute break and come back at about 20 till and get started with our speakers.

(Whereupon, at 2:27 p.m., a recess was taken.)

DR. BROWN: For the members of the panel, if I could just reiterate that when asking questions of our invited guest speakers, who are very knowledgeable in all of these issues that we're talking about, if one can maintain the question relating only to the exact specific details of the

presentation that they are making, rather than trying to generalize it to questions that we may be asked to puzzle about tomorrow, that would be in the best interest of the agency.

If a question that you have relates, in some way, to clarifying something that was stated during the speaker's general presentation, such as slide 18 or something specific, then that is perfectly fine. This relates not in any way to anything I think more than the issues of real or suspected conflict of interest that we have to deal with.

We want to move ahead with our speakers now. And our next speaker is Dr Chris Feudtner from the Children's Hospital of Philadelphia.

Presentation - Chris Feudtner

DR. FEUDTNER: Good afternoon. I'm Chris Feudtner, a pediatrician at the Children's Hospital of Philadelphia, who cares for children with complex chronic conditions, including when needed, the provision of palliative care. And I've spoken to -- not at this forum, but a similar prior

meeting -- about the issues around opioid use in pediatric palliative care, but I'm saying that to say I'm not talking about that today.

Today, as a pediatric ethicist, which I also am, I'm focusing on a very specific issue that is part of the deliberation going on in the room about the response to the opioid misuse epidemic and how that should or should not factor into decisions about how to study opioids and how to label them, particularly that issue of labeling.

I'm not going to be talking about the ethics of trial design or other aspects of again issues that you are having to grapple with, but very specifically about labeling.

I'm going to reiterate points that I made the last time I spoke because they're ethically relevant. It's important to emphasize at the beginning that, as a pediatrician, as an ethicist focused on the wellbeing of children. And there are two groups that I'm keeping my eye on, namely a group of children, adolescents, young adults, who take opioids in a prohibitive and harmful manner.

The second group are children, adolescents, who are at risk of experiencing inadequately relieved severe pain, and that to serve both of them, the public policy challenge is to come up with a balanced policy response.

The main point that I'm going to make in the talk, though, is that there needs to be clarity about what labeling is trying to do, and I'm going to cut to the chase. Labeling is not trying to strike this balance. Labeling has a fiduciary interest of providing evidence-based guidance for individual-level decision-making. Let me see if I can support that claim.

Labeling, as I said last time, is an intermediate step between the science that is done on drugs and how to use them, efficacy, safety, and clinical practice. It can provide a means of taking very disparate modes of practice, and through labeling help to consolidate them and make them more effective.

Labeling, as I said last time, can provide both a confirmation of the best practice, the most

evidence-based practice, as well as to constrain practice to say there are other ways of using these drugs that are not to be employed.

The labeling of OxyContin exhibited both of those characteristics, both a confirmation and a constraint. On the one hand, as a confirmation, it said for the set of patients who are 11 years of age and older, can use this medicine if the following conditions are met. They have to be opioid tolerant. They have to already be receiving and tolerate a minimum daily dose of opioid equivalent to 20 milligrams of oxycodone orally or its equivalent. That's a constraint. That means that first-time opioid naïve patients should not be given this drug.

Now, there was a lot of concern at the time that the labeling was passed that there might be a boost, if you will, of use of OxyContin because it was now pediatric labeled. Well, there's clear evidence that actually came out as I was preparing this talk, that that was not, let me emphasize not, what has happened.

Study reported, just out in JAMA Pediatrics, underscores the constraint effect of labeling. When they looked at OxyContin prescriptions in large data sets over the last several years, they can see a clear -- admittedly not a striking, but a diminution of the amount of OxyContin that is being prescribed after labeling went into place. I think that's a very important point. Labeling in this case, it turned out, had a diminishing effect on the use of OxyContin, particularly in the group 11 to 17 years of age.

Now, beyond that, what are some of the ethical insights and implications of this focus on labeling as a response to the opioid epidemic that we should be thinking of as we weigh and balance all of the considerations that we might have going on in our mind?

Now I say labeling as a piece of that puzzle because it is only -- and I think as an ethicist one of the points I want to make, it's very important that we call out the situation and its adequate description. Labeling is but one piece,

at most a small piece, I am going to argue, of how we might try to respond to the opioid epidemic. It is imperative that we don't let the focus on opioid labeling distract us from what are probably much more effective ways of handling the epidemic.

Already some of the discussion has raised issues like prescription monitoring. That is not a labeling phenomenon. That is an activity that needs to be done outside of the labeling activity. And everything else that is on here, including as a subsequent speaker will talk about, addiction treatment, will be important pieces of managing the epidemic.

What I want to outline in the time I have is what I think of as different phases of doing a policy analysis from an ethical point of view, first to delineate, to depict aspects of this situation; then to think about what problems have we detected that actually warrant being addressed; and then to deliberate for each of the problems how we think about how we would come up with a trade-off of the pros and cons and the right action

at the level of the individual patient, at the level of populations of persons, which I'm really going to keep harping on as a distinct activity; and then the meta-issue of how does a group like this that has to somehow think are we going to try to combine these into one synthetic approach, or are we going to keep these activities separate; and then I will conclude.

There are aspects of this epidemic situation, as well as the pain situation. Both groups are in my mind. So we have patients and persons, pediatric patients in pain -- Dr. Berde and others have described clearly the wide range of patients who can be in pain, both acute pain, chronic pain, mild pain, and severe pain -- patients at risk of misuse; patients who have been prescribed opioids who may go on to develop a misuse pattern of use; and then adolescents who never have been prescribed an opioid who wind up obtaining the medication through some other method and have never been exposed.

Looking below that, there is another aspect

of this situation, which is really in the public dialogue of I would say mixing up some of the decisions and deliberations, or aspects that are really about me taking care of a given patient, where I understand that patient and his or her preferences and the problems that they confront in detail, versus the management of an overall population of patients, not patients persons, who I will never see.

Another aspect of this situation is the number of systems that have to be thought through and accounted for, the complex healthcare system. So when Dr. Berde talks about how even in the Boston system, there may be multiple prescribers, so that they have developed a way with prescription monitoring so that within house they can actually think about how that system might or might not be addressing the problems of opioid use and misuse.

We have the insurance and payment systems, which again, if we focus just on opioid labeling, we're not going to think about how the payment system and its underpayment for non-pharmacologic

based pain management, for programs such as the reflex neurovascular dystrophy, these regional pain syndromes, how they get paid for is part of the potential problem. We have the police and drug enforcement systems, and then the FDA is but one element in those systems.

Then an issue that has come up a couple of times, we have this problem that we often do not have sufficient information to weigh the individual-level risk and benefit. And a point that I'm going to try to make clear, we even have less information and less certainty about population-level impact on the overall epidemic of either unrelieved pain or opioid misuse in terms of the impact that a specific intervention would have, so that many of our thoughts about that I'm going to gently say are really very, very suspect because we have little data.

So within that overall system and situation of problems -- or of the situation, we have particular problems. We have individual patients who are at risk of suffering due to pain, and we

have patients who are at risk of subsequent misuse. And there are often people will talk about, on the one hand we have this group, on the other hand we have this group.

But those two groups of people are existing at different levels. We have individual patients who walk into the room, or are carried into the room, who are in pain. We see them, and individual prescribers are treating them. Then we have this rather ill-defined amorphous. They're real people, but we never have them under our control.

Our thoughts about what is driving their behavior and how we meet their needs is a very different phenomenon in terms of the data we would need to address what are effective interventions from them and, as I'm going to point out, the ethics of the decision making. It's very different for that group than for the individual patient.

Then I just need to call out some things that are going way beyond what you might think of as the ethics mandate. We have problems of a blame game of who is going to be held accountable for the

opioid epidemic, that tends to focus on pills and not a coordinated solution to the misuse problem.

We have problems with a few pediatric -- and one or two is, trust me, too many. But we have a misuse of deaths that occur in the pediatric setting, prompting a very specific focus on pediatric opioid use, whereas most of the pediatric patients who are misusing are not getting their medicines from a pediatric source.

So there's a conflation here that the sorrow and the anger about pediatric adolescent and young adults who die is going to be a pediatric practice problem, and I'm going to call that into question.

I've already mentioned the insufficient payment for non-opioid pain management induces a quick-fix, pill-based response. And then I've already alluded to that we don't have all the information that we desperately need to have the most optimal response to either specific level pain.

There's also this issue of how much does the risk of subsequent misuse go up if I prescribe

somebody an opioid. We have some data about that. We'll talk about that. We have the problem of not really thinking about how systems are interacting. And then as I said, we have a bigger problem of not really contemplating how capricious sometimes our trade-off is being done at the individual versus the population level.

So let me focus first at the individual level. And we're talking about a patient who has come into the room, and we're looking at the risk of pain versus the subsequent risk of misuse.

We can think about this in classic ways of thinking about multi-attribute decision making in a kind of table format, where the first goal, and it's an ethical goal, is to work with that patient, along with my expertise as a clinician, to define what are the goals of treatment, and there could be a range of them.

Obviously the patient wants to get out of pain now. They may also want to stay out of pain, not have it occur in the future. They don't want the opioid side effects. They don't want nausea,

the constipation. And they don't want to wind up having the development of opioid misuse.

The second goal is to work with the family and the patient to really define how much do each of those goals matter to them. Different types of scenarios, and I'll go through different scenarios, those preference weights may be quite different. So it isn't enough to simply say, well there's a trade-off between pain and misuse. There's going to be more than just those two goals, and how individuals trade those off may be different depending on, conditioned on their literal medical condition.

The third thing an ethicist has to make sure, and I would encourage you to do, is to think of the middle course option. The number of times -- as both an ethics consultant and as somebody who does ethics policy work, there is a constriction that we only think about option A.

Well, there is not such a thing as only an option. That's not an option, that's what you have to do. Typically there is more than one option.

Typically there's more than two. Although we tend in public policy to try to define it as there's really two options. Often there's an option in the middle, a hybrid, or additional options. And it is ethically inappropriate to allow the range of options to be restricted for no good reason.

So non-opioid based treatments -- and by this I'm not even referring to the NSAIDs, the acetaminophen, but I'm talking about the physical rehab, like Dr. Berde spoke to -- they also need to be something that is advocated for.

I mentioned how the preference weights may vary depending on the condition. So again, I have an individual patient coming in. If he just broke his leg, he may say I really want to get out of pain because it's excruciating right now. I'm not worried about long-term pain because I know that once I have the cast placed, in a day or two, I will actually be out of pain. I don't want to be nauseated. I don't want to have constipation. But right now I just don't want to be in pain. And I don't want to get hooked on this stuff either.

These are the kind of concerns that people will often say.

That's very different than if they have chronic pain. Now again, individuals may have different preference weights, but it wouldn't be unusual for them to say, well I want to get out of pain as quick as I can. I really just want it -- anything we can do to make it go away long term is like one of my top priorities. And again, I don't want to get addicted to narcotics, and I'm starting to worry more about some of the side effects.

Patients with advanced cancer, though -- and this is the group that I often am involved in, in palliative care, again Dr. Berde mentioned, it's not just cancer, it could be other complex chronic conditions that affect children in a debilitating and ultimately fatal manner -- they may be focused on the short-term pain.

They're also very worried about long-term pain. And frankly, there is such a preoccupation with pain obliterating their ability to engage in

life, that they're willing to take some of the side effects. Yes, if you can make them go away, and I'm probably going to be on these for the rest of my life, which is going to be short. So they may have a very different preference set.

Now, who is going to define that? Well, the doctor and patient are going to define the goals. I can talk about what is a feasible goal, what are goals that are other patients trying to seek. The patient is the one who largely gets to determine the relative weighting. If they don't want to weigh safety considerations at all, I can exert influence on that, like no, no, we really do need to think about the side effects and safety. But basically it's up to the family and the patient to tell us how much they're willing to place weights on these different goals.

Then the act of deliberation, as we think about the treatment options, and we say, what's the likelihood that a particular treatment option would achieve those goals.

Labeling by the FDA is providing the best

authoritative, clearinghouse, evidence-based approach to how to use the medication like opioid treatment, which I'm culling out here, but will be true for any of the medications that are labeled, so that I can understand how it is likely to be efficacious and the safety issues. And that's what labeling does for me as a provider. It's what it also does for the patient.

Let's move on to thinking about at the population level. And here I'm going to have to shift. I'm going to have to talk about populations of misusers, people who wind up misusing opioids, and the total amount of opioids that are diverted.

Now to do this, I created what I'm very quick to admit are probably -- they're simple models. They're probably incomplete and inaccurate, but hopefully they provide a little bit of enlightening as to how complicated this task is. So if you look at this and you say, oh, that's way too crazily complicated, I've made my point, but this is the reality.

So if we were to think about ultimately

moving from the largest box, which is all of the pediatric population where kids enter in and they leave when they become adults, and think about two main pathways that they become the lower right corner, a misuser, there are two ways that that happens.

The predominant way is that they just, without ever having seen a legitimate prescription for an opioid, wind up acquiring the opioid in an illicit, non-standard manner. They get it out of a medicine cabinet. They get it from a friend, and they become a misuser by that route.

The second way that it can happen is that they can be prescribed an opioid. If that happens, that's sort of the middle path, well the lowest one in this diagram, the sort of inner loop. They take that opioid for a while, and for a while, they are at risk of what I call sort of an opioid-induced, legitimate prescription induced, heightened risk. So they still have the baseline risk of becoming a misuser, but it's multiplied.

What we believe it's multiplied by is about

a third. If you look at the baseline risk of any misuse -- I'm talking about taking one opioid pill. Here's the data. If you look at people who take even one pill, or more, in their lifetime, as an adolescent or young adult, and you take that as your dichotomous cutoff of you're now a misuser if you do it one time, it's about 9 percent. So that's the baseline misuse risk.

Some might argue that that's way too intolerant, that there are people who are going to try it once or twice and then never do it again. Are they part of the opioid epidemic? Yes, but maybe they're not the ones who are going on and having the fatal outcomes or the very dysfunctional outcomes.

So I leave that up to you as to where you would draw that baseline risk. But if you take all-comers, the risk elevation appears in this paper, that if you have been prescribed an opioid, your risk goes up by about a third.

What does that mean in a population level if you were to, say, let's take the elevated risk and

we have a baseline risk of 9 percent? That means over time, these are the number of misusers you would have of that 44 million population, rather sobering numbers, over the course of a 10-year period of time.

What the multiplier effect is, is a relatively small incremental increase. So if we think -- and why is that? It's because that baseline risk is affecting all 44 million patients. The baseline marginal risk above that is affecting only the 15 percent of the population that gets an opioid prescription.

What that means is that trying to figure out how we could limit the amount of opioid prescription, legitimate opioid prescription, induced and subsequent misuse on the overall epidemic is going to have a very small effect. I mean, we're welcome to go after it, but it's not going to have a big effect.

So realize that really we're talking about the blue line, which is where it has no effect, and the next line up, which is 1.5. The data, such as

we have it, is that it's even smaller than that. So if you want to go after that little marginal increase at the population level, that's a decision to make, but it's not as big an effect as you might suspect.

What if we were to think about, well, it's because we have all these opioids going home with patients after their orthopedic procedures. We've got to get the orthopedists to stop prescribing anything because they're stocking the medicine cabinet, which is not -- I'm being a little facetious here, I want to be clear about that. But people would say that there's a problem that we're supplying the illicit diverted sample.

Again, I'm not going to go into details, but you could think about building a model. I'm not saying this model is correct or accurate, but it starts to illustrate how complicated it is when you start to think about population-level dynamics, and potentially the attenuation that occurs when you start to mix in the adult population.

This would be what it would look like to

ultimately wind up with pills, prescribed to children, ultimately wind up being diverted. They're going into a medicine cabinet. They're warehoused for a period of time. Maybe they're being disposed of properly, which would get them out of circulation, out of harm's way. If it comes all the way down, they're going to wind up becoming potentially diverted. You have rates for each of those.

The problem is that you have to also combine that. What I've done here is taken that model, and that's the upper part of this diagram. Below it is the adult population that are being prescribed opioids, and they are much more extensive, to the degree that what we're going to see is that they're going to swamp any effect that we might do by pediatric labeling as a choke point on the overall diverted opioid supply. It's just not going to work.

Recall that I began the talk by pointing out some recent data that the labeling effect of OxyContin actually lowered the rates of OxyContin

that is being given and going home into a medicine cabinet. But for the purposes of this talk, before that data had come out, I imagined that it could go anywhere from potentially being a constraint effect to potentially being an accelerator, that labeling would promote use.

Let's suppose that it had promoted use. Not what we found, by the way. What we found is that labeling lowered it. What we would have then is that the medicines, after this labeling rule goes into effect at month 6 -- so that's why you see that dotted blue line going up, is because more opioids are being prescribed, and eventually they're funneling down and they're getting diverted.

That's shown on the right axis that out of an imaginary population of 100 kids, you would start to see pills going into circulation that are in the diverted circulation or stock.

On the left side, though, is the number of pills that are being essentially diverted from the adult world and the total. The adult population,

which is far more extensive, that's the red dashed line. And if you add the two together, you can see that there is a small rise by a pediatric labeling effect, but this is going to be swamped by what is going on in the adult world.

Now, again, I wish I could have great data. I wish I could have actually pulled published papers that are doing population-level modeling. But this is the kind of work that would be required for me to do a trade-off analysis.

Let me move on then and talk about what that trade-off would look like between the individual who comes into my office, is in pain. Am I going to prescribe an opioid because it clearly could help that patient, or am I going to be constrained because of concerns about what might happen, not to that patient, maybe to that patient in terms of subsequent misuse, although that's a fairly defined basically 3 percent absolute risk increase, versus what would happen to the population.

Let me walk you through the left side and then the right side. On the left side, let's

suppose that we have a labeling that goes through, and we suddenly start to have more pediatric opioids at home. We would see a rise in the number of pills that are being dispensed, not necessarily diverted, this is just more opioid at home because children need them, and we would hope to see a decrement in pain. Right? That's a positive -- that's the trade-off, more opioid at home, potentially a little bit more diversion, we're worried about that, and better pain control.

On the right side, what I'm showing, though, is that in terms of the total number of pills that are diverted per month because of this huge adult supply, that increase in pain control, that relief, that drop in pain scores, is being purchased at -- you can all see that that blue line at the top doesn't change much. That's the policy trade-off. Will you give up the decrement in pain to try to have a non-visible change in a trend line because of the adult population's use of opioids?

Again, I don't want to maintain that this is exactly right numbers or data, but it illustrates

the trade-off that at the individual level, we would have a benefit. At a population level, we may have a non-event.

What is the role for the FDA in labeling and thinking about this trade-off? The FDA can help inform what reasonable goals might be. I'm not clear what the FDA's role is to simultaneously, within labeling -- not talking about REMs or other ways of thinking about trying to modify risk, of simultaneously in the labeling thinking about the population-level effects.

I don't believe the FDA can do much of anything with the preference weights that individuals come into the office and say that they care about. They can try to emphasize and educate. Again, that is an activity that's not clearly related to labeling.

What role does the FDA, if they get involved in this, having to think about the ethics of the overall curbing the epidemic -- what does it owe that overall situation and the set of problems to not just think about the opioid treatment, because

that would be myopic and overly focused, but also to simultaneously advocate for non-opioid based treatments?

Then finally, as I've tried to illustrate, at the population level, what data and what kind of modeling do we have to rely on to know that we have struck a balance that is informed as opposed to just gut felt?

Labeling, my conclusion then, needs to be focused on the individual-level considerations and guidance, to the point of, if I state it firmly, there should almost be a firewall around labeling that it is focused on what is best for patients.

Now admittedly, when we look at individual patients, we have to look at the reference population of patients to draw conclusions about what would benefit me if I walked in. But labeling should be focused on the patient in front of me.

That fiduciary duty to provide that kind of information, where there is no contamination, as the provider I can read the label, as the patient I can read the label -- and this label is trying to

address the needs of that particular encounter, and it is not cluttered with thoughts that I've tried to point out, maybe under informed and not my agenda, that the labeling is not having these other influences creeping in, I think is an important point that I want to drive home.

This slide just gets redundant, error on my part.

So the conclusions. One is that narrow depictions of a situation and problems are ethically problematic, deeply problematic. If we think that we're fighting a small little brush fire when in fact there's a whole forest fire going on, we're going to make huge mistakes that are not going to help anybody, and are going to ultimately be hurtful. So the ethical framework for considering pediatric opioid policy needs to start with an open, forthright, full accounting of the current situation, identifying the variety of problems that are driving the opioid epidemic.

Second, simplistic thinking at the population level is also ethically problematic. It

does not convey the truth, the complexity of the situation. Simple solutions to complex problems may work, but we owe it to people to be clear that we're not really sure. And in fact, many people believe that labeling OxyContin would exacerbate the problem, a very, very, dare I say on the one hand both a commonsensical notion that turned out just not to be correct.

While individual deliberations in the office about the pros and cons of opioid therapy for severe pain is demanding, and often again we wish we had better data, the deliberation regarding population-level implications is orders of magnitude more complicated and less certain. And while the pursuit of benefits and non-harm is still important, we need to remain aware of our uncertainty about actions at the population level that would optimize the goals that we have.

Next, solving population-level problems on the backs of vulnerable individuals is ethically problematic for justice reasons. Again, if I go back to my little graph where we have a few extra

pills that are being diverted and pain scores that are reduced for individuals who are suffering with severe chronic, or even severe acute pain, to say that we're not going to allow those individuals to have adequate pain relief because of general concerns, so for the greater good we are going to sacrifice their pain and comfort, is deeply problematic.

It's a classic slippery slope argument. An argument, that frame that we often talk about that usually doesn't apply, but here it would be best for these patients to get the opioid. And we're not doing it for some notion of a greater good that we're not even sure would be advanced. I've tried to undermine the notion that we have great clarity as to what would actually curb the epidemic in terms of doing anything that would actually be on their back.

The last point is that expanding the purpose of labeling beyond individual-level guidance to include population-level considerations erodes patient autonomy. Labeling should be exclusively,

and I use this word fiduciarily, focused on the interests of the patient who is seeking care and potentially going to ingest that drug or have that device implanted in him or her.

It should not be thinking about and allowing to intrude in a host of other considerations. It really undermines the ability to interpret that evidence condensation in the label in a way that can guide individual-level deliberation. Thank you very much.

DR. BROWN: Thank you, Dr. Feudtner.

Our next speaker is Dr. Steve Weissman from the Medical College of Wisconsin.

Presentation - Steven Weissman

DR. WEISSMAN: Good afternoon, everyone. I'd like to thank the organizers from the FDA and the various committees for inviting me and giving me the opportunity to discuss one of the conundrums that vexes me on a daily basis, which is the challenges of conducting opioid trials in pediatrics.

As way of introduction, I'm a pediatrician

through my first residency, and then I became a pediatric hematologist/oncologist. I began focusing in on the management of pain in children with cancer, and mostly sickle cell disease, and hemophilia when there was a lot of pain associated with it. A large part, due to one of the prior speakers, Dr. Berde from Boston, he and a colleague there convinced me to retrain in anesthesiology, which was the best thing I ever did.

I spend about 80 percent of my time doing clinical care in both acute and chronic pain in children. We have one of the busiest outpatient pediatric pain programs in the country. And we service the appropriate number of children in a 300-bed children's hospital that does about 26,000 anesthetics a year. So we have a very robust practice.

On a personal note, and what really drives the bus, is that I, besides having eastern European grandparents who said I had to become a doctor when I was probably two, I unfortunately suffered through the death of my younger sister from

hepatocellular carcinoma at a time when home care was not common, but our family took care of her at home. And that is what drives my bus. It's that, as Chris just said, that individual patient and how do you help them get through challenging times. And that's my passion in medicine.

I also want to be clear that even though I'm talking about opioids, our program, as many others, focuses in on using other methods of treating children in pain. We include obviously NSAIDs, various adjuvant medications, most of them of course off-label. Interventions like cognitive behavioral therapy. We have a very active acupuncture program, again with some soft evidence that it's helpful. We have a biofeedback program. We use massage, music therapy, child life, et cetera. But today we're going to focus on investigation concerning opioids in pediatrics.

These are my objectives, but I'd like to expand them a little bit as you look them over. I hope my talk is relatively straightforward. Number one, there aren't a lot of disease models that lend

themselves to the study of pain in children. We don't have bunions, and we don't have, younger kids, certainly wisdom tooth extraction, two of the classic models that have been used over the years to study acute pain. I'll show you some of the diseases we have the opportunity to study, but as I show them to you you'll see that it's a challenge.

Trial design, which has classically been based on placebo-controlled trials, we've already discussed is a challenge, and is in most people's opinion unethical in children, straightforward placebo-controlled trials.

Another challenge, not represented by Dr. van Bosse, but surgeons still underestimate pain in their patients. They undertreat them, and they don't want their patients to have opioids and interrupt our ability to get to patients to study them in various pain trials. Parents are reluctant to enroll their kids in trials, and I'll talk about this a little bit later as well.

Very importantly, we do not see the same chronic pain models in children that we see in

adults. That's crucial because it starts to create the challenge of having drugs that come through the pipeline and receive adult indications for different pain problems, and none of them apply to children. We don't see trigeminal neuralgia. We don't see diabetic neuropathy, et cetera.

So the challenge, obviously, as the agency designs trials, you're stepping into very complicated waters because the only way to potentially study some of these issues is really going after what will be off-label indications.

Long-term opioid studies often require long-term opioid use. Guess what? As you've seen a little, and I'll show you some more, we don't have patients who are on long-term opioids, not a robust population that will lend themselves to easy investigation.

Then the last issues are, we don't have that many centers across the country that are able and capable of doing these trials. And those same investigators are reluctant to embark upon getting themselves involved in opioid trials, as I'll go

over at the end of my presentation.

So why is this important? This is a 3 and a half kilogram baby who was born with a large left congenital pulmonary adenomatous malformation who had a lateral thoracotomy for resection. Pain was managed beautifully with the placement of a thoracic epidural catheter, treated with a mixture of local anesthetic and opioid. The baby was successfully extubated and was ready to begin oral analgesia.

Tell me what the safe and effective dose of oxycodone is to administer to this baby, who is already receiving acetaminophen and off-label ketorolac to help with pain, and the baby's pain score is 8 out of 10. We need sound scientific data on the efficacy and the safety of opioids in and across the pediatric age population, and we've heard various versions of that.

This is a widely circulated slide of what analgesics we have indications for in children, and they remain surprisingly small. I won't belabor the point. We've really talked about that. But

remember, as you've already heard, our patients are special populations. We have neonates and infants that we started talking about earlier in the day. Children and adolescents who probably, in relation to the last speaker, fall into the group at risk, most of our patient population, for diversion, misuse, et cetera.

We deal with a significant population of patients who have developmental issues or cognitive impairment. In fact, at an average children's hospital, about 8 percent of the patients serviced have significant developmental delay and cognitive issues. That's almost 1 out of 10 of our patients. Then we also have to deal with issues related to breastfeeding and that group of patients.

We also largely deal with very critically ill patients. You don't go to the hospital when you're well, generally speaking, as a child. And kids, remember, don't have the degenerative diseases that bring most adults into the hospital, or to the clinic, if you will.

We're also in the middle of -- and no talk I

give can take place without me making a statement about gun violence. We have to do something about it. I never in my earlier career took care of the number of kids that come into the hospital who have massive life-threatening injuries from gun violence.

That's obviously not the purview of the agency right now, but those are a special population of kids. They are often socioculturally different than many of us in the hospital setting. And they suffer significant post-traumatic stress however they got there, whether they were part of an episode of violence or whether they were accidentally injured.

We also have an exploding population of substance abuse in teenagers who are coming in as well. And lastly, depending on what happens in the next few months, we'll either have a lot of immigrants or we won't. But those are issues that confront us when we're dealing with developing populations to study in these trials.

What children, for example, can we look at

to enter into acute pain trials? These are data from 2012, the most recent available, and it looks great. About two million kids a year have surgical procedures in the United States. And you can see the age parsings are not very user friendly, below 1 and then 1 to 17, and it's about two million, both ambulatory and inpatient surgical procedures.

But if you actually drill down and you look at what diagnoses might be amenable to investigation, you really start to stretch. When you look at the under 1 age, these are, on the left side, the rank in the order of incidence of procedures. You can see that in any of the surgical groups that you might study, there are literally across the country just a few thousand patients in any of these categories.

Then when you move up even, in the 1 to 4 age range, where these data are parsed in discharge hospital patients, the numbers go up a little, but the main diagnosis is tonsillectomy and adenoidectomy, which may or may not be a great model to use for acute analgesic trials.

If you look at the ambulatory surgery group, again another patient population that will be very difficult to actually study and collect good data on, because they're ambulatory patients, they're going home usually the day of surgery, you can see the numbers are pretty low; inguinal hernia with femoral incisions or laparoscopic hernias, a lot urology procedures. And again, look at the numbers. They're actually very small. These are national numbers.

If you look at tonsillectomy, it's a robust group of patients, but again it's unclear whether they would be the best to study, and certainly would be challenging to study in an opioid trial at home.

Dr. Walco earlier alluded to the Pediatric Research Network for Pain that I participate in as one of the executive leaders in that group. This is a fairly current list of participating institutions. It's a little over 30 institutions, five of them are Canadian institutions. And when we have queried the group and met, at any given

time, maybe 10 or 12 are ready and willing to participate in acute opioid trials. And this is, again, a subset of the greater number of children's hospitals that certainly number toward 150 in the United States.

Now when you shift a little bit and start looking at what might you study in the chronic pain world, this is a typical classification of adult pain problems. And as you scan down through this list, you'll notice there really are hardly any diagnoses that apply to our patient population. And that is accentuated by a review that was published just a few years ago that looked at what are the prevalence and types of chronic pain that are seen in children.

The kinds of pain we generally see are headache, abdominal pain, some back pain, but remember this is not degenerative, easy to identify pathology back pain. It's general musculoskeletal pain that is very different from the kind of back pain that is often studied in adults. Many of our patients come in with multiple pain complaints that

fit more with a pain amplification syndrome rather than a specific disease-based pain diagnosis.

When you look at our specific patient population, we average about 500 new patients a year that are referred into our outpatient pain center. Thirty percent are kids with failed headache. Twenty percent are kids with recurrent abdominal pain, some of whom have discrete pathology. But the general type of patient that we see who does have discrete pathology who might have inflammatory bowel disease, for example, or celiac disease, trust me, they don't get referred in if their scope show that they have active disease. These are all the kids that get referred in who have been looked at very carefully by the gastroenterologist, and they can't find any cause for their pain.

About a quarter of the kids have, again, this generalized back musculoskeletal pain. Fifteen percent, I always say when I'm telling folks about our patient population, they're all the patients you think we're taking care of. So in

this group are our kids with different disease-based pain. Hereditary peripheral neuropathies are a good example, Charcot-Marie-Tooth patients who start presenting in their teenage years.

Surprisingly, as at Dr. Berde's center, we see a fair number of kids with complex regional pain syndrome type 1 who may or may not be good models to study when you think about neuropathic pain.

Surprisingly, even though it was the reason I personally went into pain, cancer and sickle cell, the truth be it is that because of changes in treatment, particularly in the world of sickle cell, hydroxyurea has revolutionized sickle cell management.

We've even published papers on how our sickle cell program, which follows about 450 kids, how beneficial it was for them to refer their patients to our program to help with prospective pain management. We published a paper about that.

I honestly can't think of the last time a sickle cell patient came to our clinic. We went

from following 40 or 50 kids in the pain center. Now I can count on one hand how many kids we now follow in the pain center with chronic sickle cell pain. It's so fantastic to see that, it really is.

So I think you get the picture. When it comes to any chronic pain indication, particularly with opioids, I'm not sure who we could study.

Now, folks, largely led by Bob Dworkin and Dennis Turk, have organized lots of meetings that I suspect some people at least in the room have been part of, either through ACTTION or other meetings, looking at better ways to organize a taxonomy, and then to create the proper models to study pain.

They've proposed six dimensions that ought to be part of putting together any kind of originally chronic pain trial, and now they're in the process of working on a similar language to direct acute pain trial.

The first one is having obviously a core set of criteria for a disease or an event. One of the problems we have in pediatrics is that kids under the age of 8 really cannot describe what their pain

type is. They are unable to give us discrete ways of letting us be informed about what kind of pain they're having.

Instead, when you think about kids, we're going to be stuck with an incident-based model, such as picking appendicitis or strep throat for example has been something that's been looked at in kids, or specific kinds of trauma, other specific kinds of surgery, like tonsillectomy as I mentioned, or herniorrhaphy. Or there have certainly been robust literature developed on how to manage needle pain, or biopsy pain, or lumbar puncture, or bone marrow aspiration in kids.

It gets fuzzy when you start going into disease groups like cancer because, again, the different types of cancer are so diverse in pediatrics. And then treatment related pain issues do sometimes lend themselves to treatment, but I will share with you that working with cancer patients in active treatment protocols makes them almost unapproachable when it comes to any kind of analgesic trial.

So you could identify a group of kids with clear cut vincristine neuropathy, but they are not going to be participating in clinical trials looking at how you could better manage vincristine neuropathy, for example. And in addition, they have such aggressive protocols, and such dynamic changes in their pathophysiology and biology, that it would be very hard to ferret out a signal that clearly would be helpful in a pharmacologic study.

Now the next one relates to host and risk factors, and I wanted to just put up an old slide from a study that we did and published back in 1998. Very quickly, if you look at the first point marked "study," in this study, it was done long enough ago that this was a true placebo-controlled trial of oral transmucosal fentanyl versus a placebo lozenge for bone marrows and spinal taps in kids. And you can see in the first point marked "study" what the average pain scores were.

In the subsequent procedures, procedures 1 to 4, a hundred percent of the patients got active drug. And what was absolutely mind blowing about

this project was, as you can see, all the patients that got placebo as their first treatment, even though they subsequently got active drug in subsequent procedures, their pain scores didn't change.

There's something different about our patient population that relates back to prior experience. I mean, it may be true in adult populations as well, but this is a major confounding issue when you're looking at pediatric patients.

The next quality is the pain quality. Again, I alluded to that, that we can't even categorize this in the acute pain domain in children, and it's going to be impossible to categorize it in some of our at risk populations.

The environmental context, if you look back on the old literature about pain and cancer treatment in children, and this is work, I kid you not, done back in the '70s at actually Boston Children's Hospital, and you look at what were the sources of pain during treatment for cancer in

kids, it has nothing to do with mucositis. It has nothing to do with vincristine neuropathy. It was all about the needle pokes that they were getting back then.

So the context, the environmental context in which kids are subjected either to their illness or their procedures really has a major impact on how they perceive pain and then certainly confounds what we might do in terms of studying them.

Then we've already talked about the fact that pathophysiology might be similar in a thoracotomy in a child versus an adult, but we don't again see diabetic neuropathy. We don't see the same illnesses across kids.

Lastly, it's very hard, unless you start to create cohorts that are age-based, AKA developmentally based, that would allow you to evaluate the impact of pain function, like how does pain and then how does pain treatment affect function. Because obviously our patients fall into different categories of functional ability.

I'd then like to shift and talk a little bit

about what I call the six Ps, which are -- it could be the six pillars of impediment to doing trials in kids. I already alluded to parents. It's hard to access them.

IRBs locally make it very challenging at times to access patients. You need extensive networking at your institution to get out and be able to touch these patients. If it's an acute post-op study, you rely on the surgeons to present to the families that you're going to be doing a trial, and they need to invite you into the room, if you will, so that you can go over your potential analgesic trials.

An interesting thing came up in a recent study that we put through the IRB, where this is for an oral analgesic that would be used after the patient shifted off of parenteral opioids, largely PCA. The IRB would not allow us to talk to the teenagers because they were under the influence of opioids, which is not unreasonable if you really dig down and think about it.

That created a major barrier because, again,

that means we need to prospectively somehow identify patients. And obviously a very common procedure that would lend itself to an oral analgesic would be kids having appendectomies, but you can't predict when kids have their appendix taken out.

I already alluded to the physicians that underestimate pain from procedures and diseases. We talked about how placebo-controlled trials generally are not acceptable, although as I get towards the end of my talk, I will talk about some models that we can use.

Many drugs are formulated as pills, but remember, you have to be about 8 before you can reliably swallow pills. That excludes a giant portion of our patients.

Kids will not allow you, nor will their parents, to do extra phlebotomy to get blood samples. They won't allow you to do finger sticks or heel sticks to get extra blood samples if you're trying to collect PK data. I mean some will, but that's quite unusual. And then I already alluded

to the fact that to date, some of the chronic opioid trials require extensive periods of pretreatment, and therefore you can't find patients to enroll in these trials.

Now, Dr. Walco and I recently reviewed data from Seattle Children's Hospital that looked at opioid use in children. Over 8,000 unique patients were identified; 43 and a half percent of them during their hospital stay received opioids.

These are the patients who received opioids for greater than 29 days, the chronic opioid population if you will. And you can see, the largest group were kids with cancer, and pretty much everything after that are ICU patients. And of the total cohort, only 132 out of the 3500 plus received true chronic opioids for 29 days or longer.

Now, we participated in two completed chronic opioid trials, and I'd just like to share some of the challenges with you about them. The first one was many years ago, was a transdermal fentanyl trial in patients 2 to 16 years of age.

Sixty-six sites were involved to recruit 199 patients, of which 173 completed it. A bulk of those patients were, as I recall, in foreign countries as well. Recruitment was very, very challenging.

More recently, so the trauma was more severe, was the recent oxycodone ER trial that required 101 sites in 15 countries. Only 44 of the 101 sites enrolled. So step back and think, like what's the motivation for a site to participate in a trial where they're likely to not enroll any patients. The cost to the site is non-compensable, is the best way to put it.

In this trial, 173 were recruited, 155 completed. This trial was unique because the agency allowed recruitment after only five days of opioid exposure. So imagine if opioid exposure had to be longer. It took four years to recruit these patients, four years, with this robust of an investigative team.

One of the targets of the study was getting to the 6 to 11-year-old age group. And as I

understand it, part of the reason that the indication for extended-release oxycodone stopped at 11 is because these data were not adequate. The target was 40 percent. Only 17 percent of the patients were in this age population, and there really weren't enough patients to allow for conclusive decisions to be made.

What can we do in terms of analgesic trial designs? There appears to be -- largely derived from the consensus conference that you've heard about now several times that Dr. Berde published in 2012 -- that we need PK data. We need dose response data. We certainly need safety, toxicity data across all the ages.

We've talked a number of times already about what to do with efficacy and the notion of extrapolating over two years, and nonetheless needing it under two years because of all the differences that people have spoken about. And that's with drugs that have known mechanism of action. In drugs with unknown mechanisms of action, it's likely that all of the above needs to

be collected if we're going to do these trials.

The model that was proposed as a result of the consensus conference is a PCA rescue model, or an NCA, nurse controlled analgesic, rescue model. So that all patients have ready access to opioids, it allows for the use of a placebo and an active drug, and all patients then can be immediately rescued. And you look at the decrement in opioid use using this model.

Somewhat controversial, but Dr. Kossowsky and Dr. Berde published a paper just last year in Anesthesiology where they went ahead and looked at published literature, looking at four classes of drugs: opioids, NSAIDs, acetaminophen and local anesthetic.

They pulled together all the papers that used an opioid-sparing model with immediate rescue to see if indeed the model held up. And their review pretty conclusively shows good sensitivity and tolerability in terms of using this model.

This certainly will lend itself to most acute pain models. Remember, though, that it's

complex because it requires the use of technology, a PCA pump. It's going to restrict studies to patients in the hospital, which certainly in our younger age group is probably appropriate anyway.

Now, the last thing I'd like to touch on is what I label the inherent risk to investigators. And I want you to understand that I, and many of my colleagues, have had lots of dealings with pharma along the way related to the proper application, development, and design of clinical trials for opioids in pediatrics. We're not subservient to pharma, at least in terms of my interactions with people who do this kind of work. We genuinely are trying to figure out a way to do these studies.

As Dr. Havens alluded to right spot-on -- people from Wisconsin are usually right spot-on -- and Dr. Walco alluded to, we cannot find other funding sources to do these studies. This is a real challenge. They're not going to get done unless we can make this enough of a priority that there are monies available outside of pharma to do some of these studies.

The challenge is that when these projects get done, many of the investigators get eaten alive. In fact, at an extreme, the PRN pain group was ready to launch a trial of oxycodone for acute pain in patients 6 to 24 months of age.

We had a consensus conference on that. We developed a protocol. And as a group, we decided to put it on hold because of fear of the media, if you will, potential repercussions and the tainting of us individually and as a group, and we're still struggling with how to proceed with that particular trial. We do. We struggle with this on a daily basis, if you will. And the problem is, if not us, then who is going to provide the knowledge and the expertise to help develop these trials for kids?

To conclude, when you look at these trials, they're very challenging. These are not going to be easy trials to do. Patient recruitment is hard. Based on how studies are designed through the regulatory environment, that creates challenges. There are significant costs. And as I said, there's no clear source of funding for these

projects. And as I alluded to, the sites that can do these trials are sparse, and they're fearful of the negative media representation of their work.

So in the end, who suffers? And I'd like to end by quoting Primo Levi. "If we know that pain and suffering can be alleviated and we do nothing about it, we ourselves are the tormentors." Thank you.

DR. BROWN: Thank you, Dr. Weissman. That was a very nice presentation.

Our next presenter, Dr. Sharon Levy from the Harvard Medical School and the Boston Children's Hospital, who will be talking to us about opioid misuse and opioid use disorders in adolescents.

Presentation – Sharon Levy

DR. LEVY: I thank you. It's such a big room. That's actually a long walk to get up here. So I'm going to switch gears a little bit and talk about -- well, we've been talking about opioids and opioid misuse all day, and of course the opioid addiction epidemic has been a backdrop to much of what has gone on. But I'm going to address it

directly.

I am the director of the Adolescent Substance Abuse Program at Boston Children's Hospital, so I take care of lots and lots of adolescents and young adults who have developed opioid use disorders, and I'm just going to give you my perspective on the problem.

It's a little picture to remind us. Opioids, of course, has been what we're talking about, what the considerations for the FDA are. For our patients, we see a lot of patients who are misusing both opioids and sometimes opiates, or the naturally occurring products, such as morphine and heroin.

There is certainly a pathway where kids start with an opioid because they're generally more accessible and considered to be safer, and then will move on to opiates because they're less expensive and typically more potent. So that's a typical pathway. To the body and the brain, it doesn't matter whether you've used an opiate or an opioid really because they both bind the same

receptor and cause the same effects.

Now, it turns out that there are a couple of different distinct areas in the central nervous system that have high density of opioid receptors, and I've pointed them out here on this diagram. I think that this is review for most of the people in the room, but I point it out because I think that there are some important points to make.

Most of what we talked about, most of the previous speakers were talking really about opioids and their effect on the spinal cord where they relieve pain. What I'm concerned about is really the binding up here on the limbic system, and in particular the area of the brain called the nucleus accumbens, that is home to the pleasure and reward center and the prefrontal cortex.

It's these areas where binding results in the opioid use disorders and addiction that we're talking about. And of course we're all concerned about opioid binding in the brain stem because that's the area of the brain that's responsible for overdose and death.

Now, the opioid system is very dynamic, right, so I think it's probably common knowledge in this room that patients who are in pain, even patients who are opioid naïve but are in pain because they've just suffered acute trauma, can actually tolerate much higher doses of opioids, presumably because receptors on the spinal cord are becoming available with tissue damage. And so that area of the nervous system actually can act like a sponge, so you're getting pain relief without getting binding to these other higher areas of the brain.

So you're not getting necessarily the euphoria. You're certainly not getting the overdose. You may get a little bit of binding in these areas, but you're not getting that euphoria that we're so concerned about or the respiratory suppression at levels that we're really concerned about.

Now of course, the nervous system is also dynamic in that with chronic or repeated exposure to opioids, cells will become relatively less

responsive to them. So I've shown on here, actually by having more receptors come -- so it would take more opioid and more binding on more receptors to get cells to activate after long-term exposure, and of course this is responsible for the phenomenon of tolerance.

It's also responsible for withdrawal because when we stop opioids after a period of this kind of recalibration, what happens is that the normal level of endogenous opioids no longer are adequate for normal levels of signaling, and so patients start experiencing the symptoms of withdrawal, which is one of the big problems in the population that I take care of because it leads to drug-seeking behavior.

Now, we use a lot of terms. We talk a lot about opioid misuse, we talk about opioid use disorders, and we talk about addiction. And sometimes we use them interchangeably, but the differences are important.

When we talk about opioid misuse, typically we're talking about any non-prescribed use of

opioids, so that could be somebody who took more than prescribed because they felt their pain wasn't adequately treated. It could be somebody who took somebody else's prescription. And that could be either to treat pain, right, they had a headache and so they went to a friend and got an opioid medication and took it, or it could be for recreational purposes. So those are all types of misuse.

Now, just because you've misused an opioid doesn't mean you have an opioid use disorder. Actually, there are formal diagnostic criteria that appear in the Diagnostic and Statistical Manual of Psychiatry on how you meet criteria for an opioid use disorder. And they're classified as mild, moderate, or severe, depending on how many of the criteria that you meet.

Then finally, there's this concept of addiction, and that is not exactly analogous to opioid use disorder either, and there's overlap. But addiction is really more of a behavioral syndrome where there's a loss of control over

substance use and recurrent use, often even when beyond the point where it's pleasurable, but there's kind of a compulsion to use substances.

So how we get from misuse to addiction is obviously a big problem, and we want to prevent that pathway from happening, and I think that's largely what we're trying to think about.

Now, I want to start with a basic concept that adolescents are developmentally primed to use drugs. So during adolescence, during the teenage years, individuals are more likely to use drugs. And that's not just a social or cultural phenomenon, that is actually a neurologically driven, developmental phenomenon, and I'll show you what I mean.

This is just a picture of the brain of different age children. And I've pointed to 10 years because somewhere between 10 and 12 years old, the brain will actually reach its adult size. So for a long time, children were considered to enter adulthood sometime around 12 or 13, and we see that historically. And we know the story of

Romeo and Juliet, they were considered adults. They were about 13 years old.

We know that a lot of religious ceremonies, including the Jewish bar or bat mitzvah happens at 13. This was considered the age of adulthood in part because that's when growth, at least by weight, is complete.

Now, this is a slide, if you just go to Google image and you type in adolescent, these are the pictures that will come up. So I put them here on a slide for you because I think when you just get the gestalt of looking at this slide, you really very quickly understand that adolescents are really different from adults, despite the brain weight being the same. So what's going on here and how did we miss that for all of these years?

This is a slide of brain development, and what we see here is brains at birth have few cells and few connections between them. The first stage of growth, what happens is you get both more cells and many, many, many more connections between them. And then in a subsequent stage, we actually get

pruning.

Now, when I first saw this slide, I thought oh, my goodness, we peak intellectually at age 6, that can't really be good for the species. But that's not really the right interpretation. So really what's happening is the brain, in this state, is really configured for learning. And we talk about that all the time, talk about you want to learn a language, do it when you're 6. You want to learn to play the piano, all of those things, whereas the older brains are really more configured for proficiency.

So you want to learn a language, do it when you're 6. But if you want to be a great orator, you're going to need to do it when you're older. And what happens between these two stages is that the connections that are not needed are pruned away, the connections that are left become stronger, larger, more robust, and then myelinated so that they conduct signal transduction much, much quicker, and you get more proficient at the different skills.

Now of course, this doesn't happen in every part of the brain at the same time. There's this orderly progression. This is a famous slide that looks at brain scans. You can see that blue is mature brain, and then the greens and reds are less mature. And you can see that there's generally a back to front progression of this maturity, with the prefrontal cortices of course famously maturing last.

This process is really thought to really come to conclusion somewhere in the mid-20s, so this slide only goes out to age 20. You can see there's still a fair amount of green. I lost my patient here, so it's a complicated slide.

But as a developmental behavioral pediatrician, I became interested in can we look at the area of the brain that's undergoing development, and can we learn anything about behavior of children at that age by understanding what parts of their brain are most actively undergoing development.

It turns out that we can. If we look at the

first couple of years of life, the area of the brain that's most actively undergoing development is the cerebellum. And that, of course, is responsible for physical coordination and sensory processing. So during the toddler years, the part of the brain that is responsible for gross motor coordination is the part of the brain that's actively developing.

In the preschool years, we see that there's a lot of active development going on in the amygdala, which is thought to be responsible for emotional control. And again, this is when you go from your terrible twos, you went from having those toddler tantrums, into a more mature presentation, more mature way of handling those emotions right as that growth and development is occurring.

In the school age years, we see a lot of development in the part of the brain called the nucleus accumbens. It's often called the pleasure and reward center of the brain. And that is associated with development of motivation and self-sufficiency. And then finally we see the

prefrontal cortices, which is responsible for executive functions like planning, organization, impulse control, self-monitoring, those kinds of activities, develops last.

So there's a time in life when the nucleus accumbens, which I've shown here in red, is fully developed, and that's driving behavior, while at the same time, the prefrontal cortices, which is really stopping impulses and helping us self-monitor, that's not really fully online yet. It's developing, it's not proficient yet.

This correlates exactly with the time of adolescence, and it also correlates with what we observe in adolescence, which is their risk-taking behavior, and this drive to look for large rewards.

Here's a slide of a very elegant experiment. It's a little bit complicated, but it's worth taking the time to go through. So here's an experiment in which investigators had participants come into an exam room. They would do a simple task, and then they would receive a reward, and their brains were being scanned while they were

receiving the reward to see what happened in the pleasure and reward center.

Participants were broken up into three groups by age. The light blue line is the youngest children, they're 7 to 11 years of age. And you could see, whether they received the small reward, or a large reward, they made about the same response.

So this is why pediatricians will always tell you, just give your child a sticker for a reward, you don't need to go buy a big toy or take your child to Disneyworld because a sticker is actually, in a neurologic sense, just as rewarding as any of those other activities.

Now, if we look at the green line, that's adults, and you could see that their response was proportional, so small reward, small but positive response; large reward, large response.

Now look at the adolescents. With a small reward, they actually deactivated below baseline. If you've ever interacted with teenagers and how they look at you and they roll their eyes at you,

that's what that is. When my own children do that to me, I like to step back and think, "Okay, he's not being rude, it's really developmental here."

(Laughter.)

DR. LEVY: I find that very helpful.

But then look at them when they receive a large reward. They get this tremendous, tremendous firing. So this drives the systems. It drives kids to do risky things to go for those large rewards. And of course, what is the best way? If you're looking to light up that pleasure and reward center, what's the best way to do it?

Well, one of the easiest ways to do it is to use psychoactive substances because what they all have in common is that they directly stimulate the pleasure and reward system. They actually short circuit the normal pleasure systems because normally you do something that you're hungry and you eat, or it can be something more abstract, like you win a sports game, or you get a good grade on a paper, and you're going to get some pleasure. But you're not getting direct signaling. You're

getting a complicated series of signals throughout the brain that ultimately will result in signaling in a pleasure and reward center.

But you take an opioid, and that is like the express train to that kind of signaling. So it's a very easy way to satisfy what is really essentially a developmental urge, or almost a developmental need.

So if we make psychoactive substances available, it's kind of predictable that adolescents are going to use them. Not talking about any single adolescent, but as a group, you can see where there's a perfect storm by making them available. And that's why we have to be so thoughtful and so careful about things like the opioid reservoir.

This is just a follow-up. I mean, it turns out that in fact most drug use starts in adolescence, and that's totally predictable based on their neuro development.

When it comes to opioid use, we've talked a lot about kids who very young get opioids or even

adolescents who are treated appropriately for pain. The truth is that most people who misuse an opioid medication, it's not the first medication that they're trying. They almost always will have a history of tobacco, and/or alcohol, and/or marijuana use first. In fact in some unpublished data we have, from the Monitoring the Future study with over 25,000 individuals, much less than 1 percent reported use of any illicit drug without also use of one of these big three.

So when we're thinking about population-level interventions, we really have to think about paying attention to the stuff that comes first. If there's some way to prevent this or delay it or reduce it, that might be in fact one of the best prevention methods for preventing opioid misuse and opioid use disorders.

Here are some odds ratios. You can see that cigarette smoking increases your odds of misusing opioids by about 5 times, and a little over 4 for marijuana.

Not only are adolescents kind of

developmentally primed to use substances, but they're also developmentally vulnerable to develop a substance use disorder once they're exposed. Most substance use disorders develop during the adolescent time period, and that's also a function of brain development.

In fact, the odds ratio of developing a substance abuse disorder decreases by about 5 percent for every year of age. This is specifically for opioids, but it's also true and in roughly the same magnitude for alcohol, marijuana, and other drugs that have been looked at. The older you get, the less risk you have of developing a substance use disorder.

This is just a model, but I think you can think of that prefrontal cortex as somehow protecting the nucleus accumbens. So if it's not fully developed -- I mean, you think of it like that it's a roof that's still quite leaky. So it's really only after this process has developed that it's actually rare to see addictions develop in older people when substance use is initiated after

age 25.

Here are the graphs for alcohol and marijuana use. It's the same effect. And this is specifically for opioids where you can see that the odds ratio, less than 13, people who initiate misuse of prescription drugs below age 13 have over 40 percent chance of developing a substance use disorder, where at 21 that falls to less than half.

What else increases the risk of developing an opioid use disorder specifically? It turns out that smoking, either cigarettes or marijuana, increases the risk pretty substantially. I have put on odds ratios. I just want to give a heads up, I mean you have all the slides, you have the data, but some of these are culled from fairly small studies, so the confidence intervals are wide, but we've given you the point estimate for the odds ratios here. You can see, about 2 to 3 times is the odds ratio of increased risk of developing an opioid use disorder for cigarettes or marijuana.

Here's the paper that this came from on

tobacco. And just to say about marijuana, there are special considerations. We often talk about the cannabinoid system and the opioid system as if they are really two completely different systems that are working in parallel. Actually, that's an over simplistic model. In fact, and this is a paper that looks at staining for cannabinoid receptors and opioid receptors. And in fact, they're really quite often both on the same cells.

So they're influencing one another and they're influencing the cell. And it's entirely possible and speculated that cannabinoid binding is actually changing cells in such a way that it's priming them to be more sensitive to opioid receptors and more vulnerable to developing the changes that are associated with addiction.

Then on the right side, I put some other behaviors that are associated with increased risk of developing opioid use disorders, and these are all related to exposure to opioids. So you see on the bottom, and Dr. Feudtner talked about this before, prescribed pain relief, in other words

appropriate prescribed use of opioids, it does raise the risk of developing an opioid use disorder or about a third, and that's a relatively small increase.

It has to be considered on an individual patient level whether the risk-benefit is going to pay off. In most cases -- I won't say most, but obviously there are cases, somebody with major surgery or a femur fracture or a sickle cell crisis, the relative increase in risk is probably going to be far overshadowed by the benefit you get by adequate pain control. And again, that's a decision that would be made on an individual patient level.

When it comes to unprescribed pain relief -- this is one type of misuse of opioid medication. So this is people who take somebody else's prescription because they have a headache -- it nearly doubles the risk of developing an opioid use disorder.

The riskiest, of course, behavior is when opioids are used purely for the euphoria that they

produce and recreational use. It's probably the case that when people are taking it for pain, they're taking it in relatively lower doses. When they're taking it for euphoria, they know that they have to take a high dose to get that experience, and this is a riskier behavior.

These, certainly the top two, the recreational use and the unprescribed use, are issues that we can potentially control by controlling the reservoir.

Then there are some other things that are much harder to control. Depression, anxiety, family history of substance use disorders, PTSD, these all increase your risk of developing an opioid use disorder. Of course there's nothing that we can really do about this. And they are not absolute contraindications to prescribing opioids, but they are something, on an individual patient level, that we should at least be thinking about when we're prescribing.

These are slides that I think we've even seen today, people in the room are probably

familiar with, that there was a big increase in opioid prescribing in the 2000s started to taper off somewhere around 2013, and that tapering has continued, and I think that's been the result of aggressive education for physicians and prescribers.

This of course is a graph showing us the rates of opioid misuse by 12th graders, and you can see that this really parallels rates of opioid prescribing. Now again, this is prescribing in the entire population. This is opioid misuse in adolescents, and they track together; so again, speaking to the issue of the large reservoir, which is coming from overall prescribing, not necessarily prescribing to this age group, which actually makes up just a small fraction, as we heard before.

When we look at what are the motivations for opioid misuse, this is a study that was from McCabe and Boyd. It's nearly 50/50. About 50 percent of kids who are misusing opioids are really doing so to relieve pain. And this group, one would hypothesize, is going to be probably relatively

more influenced by educational campaigns, really talking to them about this is not the right way to relieve pain, and there are better ways. And then the other half are using them to get high, and they're a little bit harder to get to.

This is a study done by the Partnership for a Drug Free America that asked kids why they took opioids, and we have coded here their responses into three basic groups. So one is because they're really easy to get. So again, the reservoir, they're available anywhere, I can just get them from a medicine cabinet.

Another reason or domain was that they're perceived to be safer than illegal drugs. It turns out that this is not true, but this is also another place where we can do some education. And then the third domain was that there were less consequences. There were perceived to be less consequences. You can claim you have a prescription. You could just tell your parents, I took an opioid, but I only did it because my shoulder was bothering me, so I took a medication. So again, these are areas that can

be addressed with educational campaigns when we're talking to patients and families.

You can see that who diverts medications, you can see that diversion is very highly correlated with the reason or the motive for using an opioid in the first place, where those who are misusing opioids because of the euphoria that it creates, or recreationally, are much more likely to have been approached to divert their medications, and they're much more likely to both give and trade their medications. And it's much smaller amounts of diversion for people who are even misusing, but misusing for pain. And we don't see really any trading of medication other than people who are using it for recreational purposes.

What kind of recommendations can we come up with? Well I think a lot of these points have been made throughout the day, so I will just say very briefly that remembering that when we're prescribing to children, there's no such thing as a safe dose. We've heard a lot today about that.

Ideally, we'd like to keep our prescribing

so that the binding is happening primarily in the spinal cord, but that is hard to do and perhaps impossible for some patients. We hope that with close monitoring we can assess for things like whether a patient is experiencing side effects or euphoria, and keep the dose lower to minimize that. But it's probably impossible to extinguish entirely.

Also, just as a reminder, the side effect profiles of course are different in children. I think we heard a lot about that today. If we are going to prescribe, we should look for the things that we know are going to increase the likelihood of developing a substance use disorder, such as other drug use, a history of mental illness, or a family history of substance use.

Again, none of these should be contraindications to prescribing, but if we know they're there, I think that we can pay attention to them and be even more diligent about the ways in which prescribing, the education we give, the types of information we give these patients about we're

going to give you this medication because we need to treat your pain, but you need to know that you're at a higher risk of developing a problem, and things like parental controls.

Here's where checking a prescription drug monitoring program in the state just to make sure that we're not actually prescribing to somebody who already has a substance use disorder and is looking for easy access to opioids, would be a reasonable thing to do.

Patient and parent education. Certainly when we're prescribing, it's really critical, and not sure that it's consistently done currently, the risks of exposures to the medications, but also the risks of holding on to the medications and having them in the house. Just to kind of pull this all together, kids are both vulnerable to drug use and addiction.

The medicine cabinet here is a really big part of the problem, that nearly 85 percent of opioids that are taken by adolescents were obtained from either a family member or a peer. And in the

vast majority of cases, these prescriptions were actually written for adult patients. So it behooves us to prescribe appropriately, assess risk, keep the doses small, keep the course of treatment short.

We've talked about all of these things. But just one other point that I want to bring up is that it's really hard to deliver this information to every adolescent and parent, so here's where we get a little bit of disconnect.

So the American Academy of Pediatrics has put out statements saying we really should be educating every adolescent and parent because, really, every adolescent is at risk of having a tooth extraction and walking out of a dentist's office with a prescription for opioids, even though the pediatricians themselves may not be the people prescribing. So we have to figure out ways where we can get this education to everyone, even when there might be a disconnect between the people who are doing the education and perhaps the prescribers.

I think I will conclude there. So thank you for your attention.

Clarifying Questions

DR. BROWN: Thank you, Dr. Levy. That was a wonderful presentation.

We have an opportunity for more clarifying questions for the guest speakers. Please remember to state your name for the record before you speak. If you can, please direct your questions to a specific presenter.

Dr. Ruha?

DR. RUHA: I have a question for Dr. Levy. In reference to slide 26 I think it was, where the graph of age of onset of non-medical use of prescription drugs, the younger the child, so under age 13, if they had an earlier onset of non-medical use, they had a higher risk of estimated prevalence of lifetime prescription.

I know there was another study that showed a 1.3 odds ratio of prescription opioid, illegitimate prescription perhaps being connected with non-medical use later. Just wondering if there was

any -- if it's been teased out if a younger age of onset of actual legitimate prescription, like if a 12-year-old gets a prescription for opioids, are they more at risk of prescription drug abuse than maybe of a 16-year-old.

Has that been determined?

DR. LEVY: Thank you. As far as I'm aware, no. That's unknown, whether exposure in early infancy is somehow different than exposure later in life. People often ask me this as a clinician, so just my anecdotal experience. We don't have a lot of people coming in with a history of having been on a ventilator and given a lot of opioids as a newborn.

Now, that's very anecdotal experience so you can't hang your hat on it, but as far as I know that has never really been looked at in that level of detail.

DR. RUHA: Even with like the younger adolescents, we don't really know, like maybe 10, 11, 12 year old as compared to like 16, 17?

DR. LEVY: I think just unknown.

DR. BROWN: Dr. Crawford?

DR. CRAWFORD: Thank you. This is for Dr. Feudtner, please. And it's for your slide, near the end 43, in the last conclusions slide. Thank you. That second bullet, labeling should be exclusively focused on providing the highest level of individual-level guidance regarding effective and safe practice.

So, I'm going to ask if you could clarify that a bit because all three of these presentations really made me think. But as I'm looking at that particular slide, I wondered if you meant in terms of patient autonomy, which is respect for persons, the labeling that would be directed to the patient and/or his or her parents or guardians, depending upon the patient's age.

If so, are you talking about labeling and a medication guide, or are you talking about labeling in a package insert? Because the pediatric ethicist in you, you have me thinking of ethical dilemmas in terms of the prescriber thinking of beneficence or non-maleficence, which might

conflict with patient autonomy. But regardless of the labeling, if it's the highest level, it could be very long medication guides and/or package inserts.

Depending upon the age, the level of understanding, how are we going to get all of that in, a little bit of overlap with Dr. Levy where she said educate every adolescent and parent, and if labeling is part of that, this could get very long and lengthy and hard to understand. So kindly help clarify that for me.

DR. FEUDTNER: Thank you for the question. The point I really want to make is what should not be in the label. So we just had a very excellent presentation about an issue that should be in the label.

If you get this opioid, there is a small, very small, potential risk that you will go on and have an opioid misuse order. And they should be counseled for that. There should be potentially risk assessment to think about how much of a magnitude.

So that's again at this individual level, so I'm taking care of you, it would be a discussion that you and I have. And the FDA's job, what I'm saying, is to provide the best highest level of evidence. I'm not asking for longer labels. I'm simply saying, stay focused on the individual level.

The labeling should not be trying to account for the fact that I gave you the opioid because you and I sat down, we thought about the risks and benefits, and basically worked out it would be the wisest course to take care of you or your child's pain.

It shouldn't be about whether that medication is going to disappear from your medicine cabinet at some point. That is another set of considerations that could be addressed by, I'm only going to give you a few days' supply, like I don't need to give you a week or longer, three days should be enough. I'm going to figure out other ways to make sure that we constrain the amount. But that's really a prescribing practice, not

really a labeling issue.

So again, in the context of what went on in the controversy about labeling OxyContin, all of my remarks were really responding to a lot of pressure that was being placed on the labeling activity to solve problems that I see outside of the purview of the labeling activity.

DR. LEVY: Could I just add on to that? So I agree. And what I was talking about in terms of educating every parent and every adolescent is largely about the reservoir problem. So we don't want kids to go in and use somebody else's medication.

So that's not something that we're going to educate them through an opioid label actually. That's education that has to be given in some other way, and we have to figure out how we can get to kids. So primary care is one possible place in which we can do that. But we want to prevent them from taking somebody else's medication. So obviously that's not something that needs to go on the label.

DR. BROWN: Dr. Walco?

DR. WALCO: This question is also for Dr. Feudtner. Chris, in looking at your analysis of focusing on the individual patient and counterbalancing that against the population of persons, if we consider abuse-deterrent formulas for opioids, virtually all of them have some, maybe small, maybe more than small, incremental potential for adverse side effects to the person to whom you're giving them.

So if I take your analysis to the extreme, I would say, just give oxycodone, don't give an abuse-deterrent formula, just give it to that patient because that's what's in that patient's best interests. Where would you put that whole argument given how you framed this?

DR. FEUDTNER: Thank you for that very important example. So first, I think the labeling for the abuse-deterrent opioids should include information, again at the individual level, about the trade-off that you are making.

So I could present again, like your child,

your adolescent, there are two versions of the opioid I could prescribe. Let's look at the labeling on the one, let's look at the labeling -- and that's not how I would counsel, but I would be counseling based on labeling-based information about here's the advantages and disadvantages of the drug that is not abuse deterring, and here's the advantages and disadvantages of the one that is.

I'm not saying that the FDA should not offer drugs that have these other attributes, but the labeling should not be squelching medicines that don't have that attribute because of the population-level implication.

In other words, the labeling can address the fact that there are advantages and disadvantages for you as a family, or for you as a patient. So in that counseling, I'm not sure why I would be prescribing your son that medication, but you could look at it and say okay, that is something I believe that we should be backing that overall national effort, and I would like to take that

medicine.

I think that it's outside of the labeling to do this weighing of whether at a policy level we should be advancing the prescription of the abuse deterring medications. And my point is simply, that's not going to be solved in the labeling debate.

I don't know exactly who the governing body is, or to the degree that the FDA is involved in that as a member of other agencies that have to be part of it. It's really whether it comes down to the act of labeling that's going to try to actually adjudicate all of that in the package insert.

DR. WALCO: So if you were to take it beyond labeling --

DR. FEUDTNER: Yes?

DR. WALCO: Because what I walked away with, and maybe this was my faulty hearing, was you were more focused on the interaction between the physician and the patient and doing well by that patient. And your tolerance for compromising what's in that patient's best interests for some

greater good of society seemed to be fairly low.

DR. FEUDTNER: I'm thinking about regulatory boundaries and about what you are trying to do as an actor in the whole regulatory scheme in terms of the duty the FDA has to individual-level patients. I believe the FDA has duties also to the public at large. But trying to solve all of that in the labeling task, all I can say is that strikes me as a very complicated synthesis with lots of input that would be required to come up with, say, the preference weights that would be required for even that trade-off with the opioid deterrent; like how much side effect are we going to impose on your child who just fractured his femur and is going to be on opioids for basically 24 hours?

How much of a potential loss of efficacy am I willing to put him through in order to prevent that small little paltry amount of medication from being diverted and wind up potentially being abused, but in this non-abuse forming -- you get my point, that that's a much more complicated task.

So I would be mindful as a committee of

overstepping either regulatory requirement, and in terms of taking on these other tasks because all the other players are sort of stepping away from it. This is really about drug regulation, beyond what I think the FDA has within the labeling mandate that it has.

DR. WALCO: Thank you.

DR. BROWN: Dr. Gerhard?

DR. GERHARD: Tobias Gerhard, Rutgers. This is a question for Dr. Levy. Well, first of all, thank you very much for the very informative talk for somebody like myself who doesn't know that much about addiction research. However, there were a few slides, kind of starting with slides 21, and then slides 25 and 26, where you basically gave what at least I heard as a causal interpretation.

So cigarette smoking, marijuana use, alcohol use leads to higher use of opiates later. Then when moving on to these graphs of age at first drink, age at first use, so higher rates the earlier the behavior starts, and then the same for slide 26, age at first non-medical use.

Maybe I kind of misheard you there because my interpretation of just looking at these slides would be to say that there are adolescents that are predisposed to addictive -- I mean to seek that reward, and are predisposed to use addictive substances, and they will pursue all of these substances.

Then the age at first use may be a proxy for the strength of that predisposition, that just the people or the adolescents that seek this behavior out earlier are just the ones with the strongest predisposition.

The kind of context for this question is that I'm kind of concerned about this interpretation that came with the first question, that this somehow then gets maybe interpreted as a reason to try to delay use of even prescription opioids, which is I don't think at all what you were saying. But I just kind of want to little bit clarify whether there are stronger arguments for causal interpretation or whether I just kind of heard you say this.

DR. LEVY: No, it's an excellent question, so thank you for asking it. I did not mean to imply that there's causation here. These are associations. And the reason that I bring them up is because they are potentially markers. So we know that there's strong association between use of other substances, and then use of opioids, and these other substances come first.

So they're a very good way of -- a very good marker for who we should be paying attention to and who we should be intervening with, potentially by getting them interventions for their substance use, which we don't know for sure that that will lessen their risk, but it may.

So that's all I meant by it. I did not mean to imply, in any way, that we should be trying to delay the use of opioids as a pain medication treatment. So thank you for asking that.

DR. GERHARD: Thank you very much. Very helpful.

DR. BROWN: Dr. Flick?

DR. FLICK: This is for Dr. Feudtner. I

think that your presentation was marvelous and very thought provoking, and I think certainly useful to me and I'm sure the committee. I wonder if you might just help me with something.

So there seems to be an assumption in the argument that you make that opioid prescribing is efficacious, number one; number two, is appropriate, which are different things; and number three, that by changing labeling we will somehow reduce efficacious and appropriate prescribing for those children who are in your group number one.

Do you get my question?

DR. FEUDTNER: Well, let me respond, and you may need to then clarify it. So clearly labeling by providing an evidence-based approach to thinking about what works, for whom, and what doses should boost effectiveness -- and it should, if it's done well, diminish the unlabeled use. So it should get rid of potentially inappropriate. So you should be, if you're thinking about the risks and --

DR. GERHARD: Well let me --

DR. FEUDTNER: Yes.

DR. FLICK: If I could stop you just for a moment. So let's be more concrete.

DR. FEUDTNER: Perfect.

DR. FLICK: So let's take the OxyContin in a post-operative orthopedic patient that we talked about. Now, we can say that's off-label use, right? And if we reduced that, would patients suffer? So we have the tension between number one and number two.

Maybe we should put that slide up. I think it's slide number 4, Stephanie. So that creates a tension between number one and number two. I might have had them backwards there.

If we reduce inappropriate prescribing, or maybe we should say off-label prescribing, have we really inhibited our ability to adequately manage pain?

DR. FEUDTNER: A couple of thoughts are going through my mind. One, the specific example of a child who has a very large spinal fusion surgery, where I'm presuming, having cared for many of them, two to three weeks of a lot of discomfort,

I can see in the individual counselling that I myself may even go off-label because of the long sustained efficacy of an extended-release formulation.

Although there may be still event-based pain episodes that are not going to be covered, I do believe that I have experiential evidence, based on basically work with PCAs, that a basal rate of an opioid can be overall opioid sparing because you don't need to have as much demand.

So I can understand a rationale, when I'm looking at a child who I expect is going to have seven or more days of pain, and I realize that that would be in variance to what the OxyContin label talked about. And I may not use OxyContin, but I can understand a rationale.

At an individual level, we could go to one of the subsequent slides, talk about the risks and benefits of opioid that is short acting and an extended release that provides some basal relief. And we could talk with the family about the pros and cons of that. I could talk to my colleagues

about whether I'm completely off.

You asked a question previously, do I have evidence that I'm right about that? I don't have a paper I could look at. Again, we often are having to operate with a paucity of evidence. But anecdotally and in terms of how we -- by analogy with PCA, I might make that argument. I might also get pushback. But that's done at the individual level.

The point that I'm mostly trying to make is even if I get it wrong, dead wrong -- not dead -- even if I'm wrong for that particular patient, and I'm overtreating with the extended, what's the likelihood that the management of that specific patient is going to have a significant impact on group one?

What my point in my talk is that group one, the people who are taking opioids in a prohibited manner, the day-to-day management of their spinal fusion cases, I think you're really having to grasp at something to say that you're going to really quell the epidemic by tightening up the control for

that specific group of patients.

DR. FLICK: Well, I don't think anyone would suggest that we're going to -- any specific labeling in pediatrics is going to accomplish that goal, nor would any specific change in labeling accomplish that goal in any setting. As you mentioned earlier --

DR. FEUDTNER: It could in the adult setting.

DR. FLICK: In the adult setting, in any setting, because this problem is broader than simply labeling, as you have I think correctly pointed out.

DR. FEUDTNER: There are examples in the adult world where opioids, say for back pain and other things, where the evidence might be that -- again I'm not an expert in that, but I'm specifically referring -- and as an ethicist, I think that we have become infected in our thinking about the opioid epidemic because of our concern about that, that it's infiltrating this discussion to a degree that you might be -- I just want to

bring awareness to. Because I agree with you that everybody is going to say, oh, we wouldn't think that labeling is going to affect the overall epidemic.

There was a lot of controversy about that last year, and much of the discussion here continues to touch on opioid misuse that isn't simply this 1.3 relative increase on a base rate that is probably about 1, 2, 3 percent. So you're talking about going up a fraction of a percent increase in your likelihood of actually winding up having an opioid misuse problem, not even an addiction problem.

DR. FLICK: Chris, again, maybe I'm missing something, but there's a continued linkage between one and two, as if one is dependent on two, or two is dependent on one. If you reduce inappropriate prescribing, you will reduce the adequacy of pain management in children. I would reject that out of hand. I think there's no data to support that. At least I'm not aware of any, and maybe others here might suggest that.

It seems that there's a tension between the approach to the individual and a public health approach, which are different things I think.

DR. FEUDTNER: Well, then we're entirely agreeing. I don't think that the needs of group one and the needs of group two should be thought of simultaneously. I think the needs of group one, the young adolescents, young adults who are winding up with opioid misuse problems and addiction problems, are largely independent of anything that this group is going to do about trying to address the pain relief needs that we're thinking about with opioids.

DR. FLICK: Thanks.

DR. BROWN: Dr. Neville?

DR. NEVILLE: I just wanted to make a comment, and I'm sure this was not meant, but for me it was implied. Full disclosure, I chair the AP committee on drugs, and we have done quite a bit of work on off-label use of medicines in children. And I just want to be clear that off-label does not equal inappropriate. As was given in the example,

OxyContin could not be labeled for younger children because the studies couldn't be done.

I think the label, as has been pointed out, is evidentiary, and in pediatrics we're stuck because we don't have enough evidence. And I just want to be clear that the point of an individual patient post-op spine getting OxyContin may not necessarily be right or wrong. And because it's off label does not mean it's inappropriate, it may mean that we don't have enough evidence to include that patient group in the label.

DR. FLICK: You're correct. I apologize.

DR. BROWN: Thank you.

DR. WEISSMAN: Can I make a comment? This is Dr. Weissman, Steve Weissman.

DR. BROWN: Yes, Steve.

DR. WEISSMAN: I think the elephant in the room for me is that the deliberations of this committee could potentially end up proceeding forward to say there's too much population risk, so therefore we don't recommend that certain aspects of opioid use in children should even be studied.

To me that's the elephant in the room. I'm not really hearing that, but that's certainly the elephant in the room, and that's where I see the linkage that Chris is trying to make a point of, quite elegantly.

DR. BROWN: Dr. McCann, did you have a comment?

DR. MCCANN: Yes. Mary Ellen McCann. This is also for Chris. I think if you look in slide 9, it's stating the obvious, but it merely shows an association. And for the last three, four years, prescribers have been educated, the public's been educated, there have been a lot of interventions other than just labeling. So I really can't buy, at this point, with this level of evidence, that this study anyway showed a constraint approach to --

DR. FEUDTNER: Okay. I totally believe -- accept your point. It certainly did not provide any evidence for the counter-hypothesis, though, that labeling would somehow accelerate use.

DR. MCCANN: Not necessarily.

DR. FEUDTNER: It doesn't provide any evidence, or it doesn't refute it, but you can't see a decline and say that unless you have some extrapolation evidence from some other site, that the decline should have been greater than this.

DR. MCCANN: I think that it doesn't tell us much of anything.

DR. FEUDTNER: Right, which would be fine, which is why I did that sensitivity analysis that I went on to, that even if you presumed that there was in fact a rise in the total amount dispensed, the total impact at the population level is likely to be with that incremental rise, and therefore with this relative rate increase of 0.33, it's going to have fairly small impact.

DR. MCCANN: The other point I would like to make is one of my children was on Accutane, and it's very difficult to get on that drug. And the labeling was scary and the prescriber information -- the prescriber consent forms that you had to go through were difficult.

I don't see acne anymore when I go out in

public. I remember what my high school class looked like, and there was a lot of acne. So I think somehow these adolescents who really need the drug are getting it. So I don't know. I'm just not as maybe wary of labeling constraints as I guess you are.

DR. BROWN: Dr. Flick, you have a retort?

DR. FLICK: I just want to remind the committee, as the chairman recalls, the discussion that we had when Zohydro came before the committee, and the committee rejected Zohydro not because it didn't meet the regulatory standards, but because the committee felt it was not in the interests of the public health.

We had a long discussion, that committee, about the difference in the role of the committee versus the agency. And the committee is not bound by -- and Chris alluded to that, is that this is a broader discussion than labeling. It crosses into a variety of different aspects of practice and regulation, whatever.

So from my own perspective, I'm not limited

by thinking of what's going to affect labeling, it's what's going to affect the public health.

DR. BROWN: Dr. Patrick?

DR. PATRICK: Stephen Patrick from Vanderbilt. Yes, I think two points, one that sort of echoes that, which is just a clarification. I think it's slide 33 on Dr. Levy's slide. It appears that oxycodone prescriptions have been going down regardless, and I think that's just in the context of the Journal of Pediatrics article. I wonder if that's true. I mean, it looks like it's true on the graph, and I think that's important for interpretation.

Then the second sort of data question, we've got this really great review of data from the National Survey on Drug Use and Health in our packets earlier. One of the conversations we've had from multiple different presenters were misuse and the source of that misuse. And it might be helpful for us too -- I can't seem to find the data on the proportion -- with the source of misuse among adolescents. And I wonder if those data are

available from NSDUH, from the folks who prepared those data.

NSDUH has a specific part about source of medication, and in the general population, there's a high proportion that get that from a friend or relative. And I wonder if that's true for adolescents because that may also inform some of the broader public health things that we're discussing.

DR. LEVY: A number of studies have looked at that. And yes, I think I have one slide in there that shows that the source from a friend or relative's prescription is the most common source. But there are a number of studies that have looked at that, that I'd be happy to -- I don't have them off the top of my head, but I'd be happy to provide a bibliography on that if it would be helpful.

DR. BROWN: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. I'm not sure my question, if it's for Dr. Nelson, Dr. Feudtner, or Dr. van Bosse. But we're having all this discussion about labeling, and who's following the

label for OxyContin and who's not. And just so I understand this for myself, I'm trying to understand, if you have somebody who has a big spinal fusion and they're in the ICU for three days on 6 milligrams an hour of morphine, they're certainly getting far more than 20 milligrams of oxycodone. So if you then send that patient home on OxyContin, it doesn't seem to me that that's off-label use.

So I guess I wanted to clarify so I understand what we're talking about when labeling, since there's so much discussion about the label in narcotics, is that situation of the spinal fusion -- OxyContin after a spinal fusion, there is some period of time that they're on IV narcotics.

I don't know if it's a semantics issue, if we're talking about opioid or opioid equivalence, but to me that's not necessarily my interpretation of the fine print of the label. If you're getting 5 milligrams an hour of morphine, that's far more than 20 milligrams daily of oxycodone.

So I just wanted to clarify that.

DR. FEUDTNER: We're looking at each other. We tend to think that you're right, Sarah, that there would be a prior period in the hospital of receiving opioids. But what's probably absent from the survey is exactly what kind of data was that patient with the spinal fusion on.

The point would simply be that extended release for that patient may actually fit the guidance, although the age limit may be a little bit different. The more general issue, and I want to clarify what I'm trying to clarify because I think we're in agreement.

It's the sensitivity that I wanted to bring to the committee of exactly the conversation you just had with the committee, are we talking about the public wellbeing, and the committee's job is to actually do the synthesis, or is the committee's job to be much more circumspect as to what we're going to be focusing on?

If you are going to try to the synthesis of what the public health and the individual wellbeing are going to be, just pointing out issues like this

where there might be a trade-off, the data on the public health impact is really very weak, and I think very prone to a bunch of biased assumptions about what will affect care.

The last thing I would say is this focus on the pediatric component, if I had all the power in the world, and I wanted to curb this epidemic, I would shorten the duration of opioid prescriptions for adults. I would clean out the medicine cabinets. I would dry up the supply where the supply is occurring in the adult setting. That would be much more likely to do what I think you're talking about, which is think of the public health.

The question then is, what is the mandate the committee has to advocate for things that are not in its purview to do. And I think if you're going to take that job on, you have to advocate for pain management programs and addiction programs that are underfunded, and for the adult world to be able to basically curb the supply that is warehoused in medicine cabinets, and clean up the inappropriate duration and opioid prescription.

DR. BROWN: Chris, I'll just have to say after being on the committee for a while now, and I think Dr. Flick can corroborate, is that our goal is to use all available information to do what we consider to be right based on our clinical acumen, our judgment, and the expertise that each individual brings to the committee.

We have a lot of information, just as we have received today. But we also come to the committee with information that perhaps we have not seen or heard today. So we take that very seriously, and I think that in general the committee always has.

Steve?

DR. WEISSMAN: Thank you. Steve Weissman. I just want to make one point, though. Even though I completely agree with everything Chris has said, there were some data presented at our meeting some time last year from the Hopkins group that showed that even with pediatric prescribing, that two-thirds of the opioid prescriptions were not being used, that the kids in fact were being

overprescribed based on ultimate use of the drug at home.

Again, I don't know how one measures that repository and how it ties in with the issues that you've alluded to, where the real skyscraper is on the adult side, but there is potentially some signal there as well. But again, I don't know -- really, my concern is, again, that balance of how that fits in with coming up with practical ways of getting these drugs studied so that we have good, sound data to actually take care of those individuals.

DR. BROWN: Dr. Kibbe?

DR. KIBBE: I'd like to make just a couple of small points. One, correlation doesn't mean cause and effect. And when you have a correlation, you shouldn't claim a cause and effect.

Second, labeling is an official way for the agency to communicate with prescribers on what it knows for sure and what it recommends the prescribers consider before they do something. We put black box labeling in when we know that there's

a dangerous thing that needs to be controlled, and we hope that the prescriber reads that and takes that into account. And there are times when we've had meetings, and I've been at them, where we've had a failure, of one reason or another, for the prescribing body and the patients to take even into account those warnings.

We're here to try to get more information into the labeling to help the pediatricians make good decisions, not to prevent them from using a drug that they think is useful. So whatever labeling we could get in would depend on us getting data from somebody. And I think our frustration, for the whole day, has been who do we get to get us the data. I wish we could send a memo to NIH and say, you've got to do these experiments, you've got the money, you got the researchers, get to work, but we can't.

So the labeling I'm not worried about. I think our ethicists nailed it. We put labeling in there to help patients and help physicians make good decisions about individual patients, and I

don't know what recommendations I could make to the agency to help them get that data. So I think that's kind of going to be the frustrating conversation tomorrow.

DR. BROWN: If there are no further clarifying questions for our speakers, let me just once again thank all of our speakers. They have given us a lot to chew on. I appreciate every single one of them for taking their time and effort to come here, and it's really been a wonderful experience to hear from all of you.

Before we adjourn for the day, are there any last comments from our friends at the FDA?

DR. HERTZ: No. Thanks to everyone, and really looking forward to tomorrow.

Adjournment

DR. BROWN: So the meeting for today is adjourned. Panel members, please remember that there should be no discussion of the meetings topic amongst yourselves, with any member of the audience. Please take all your personal belongings with you as the room is cleaned at the end the

meeting day. All materials left on the table will be disposed of. We will reconvene tomorrow morning at 8:00 a.m.

(Whereupon, at 5:03 p.m., the meeting was adjourned.)