

FOOD AND DRUG ADMINISTRATION (FDA)

**JOINT MEETING OF THE PEDIATRIC
ADVISORY COMMITTEE (PAC)
AND
DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE (DSaRM)**

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

September 26, 2019

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CALL TO ORDER AND INTRODUCTIONS

DR. WADE: If everyone could please take their seats. I'd first like to remind everyone to silence their cell phones, smart phones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Sandy Walsh, if you could please stand. Thank you, Sandy.

As we welcome everyone here today, I'd like to start by going around the table for introductions and ask all members, consultants, the FDA panel, and the DFO to go around the table and state their name into the record. We can start here on our left.

DR. SLEEPER: Lynn Sleeper, Boston Children's Hospital.

DR. HOLUBKOV: Rich Holubkov, University of Utah School of Medicine.

DR. KULLDORFF: Good morning. I'm Martin Kulldorff. I'm a biostatistician at Harvard Medical School and Brigham & Women's Hospital in Boston.

DR. HABEL: Hi, I'm Laurel Habel. I'm an epidemiologist and Associate Director of Cancer Research at Kaiser Permanente Northern California.

DR. CZAJA: Hi, I'm Angela Czaja from Children's Hospital of Colorado.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, pharmacoepidemiologist from Harvard School of Public Health in Boston.

DR. ORTIZ-AGUAYO: Roberto Ortiz-Aguayo. Associate Chair, Department of Psychiatry, Children's Hospital of Philadelphia.

DR. MCGOUGH: James McGough, child psychiatrist, UCLA.

DR. PERRONE: Jeanmarie Perrone, Emergency Medicine and Addiction Medicine in the Hospital of the University of Pennsylvania.

DR. MEISEL: Steve Meisel, Director of Medication Safety for MHealth

Fairview in Minneapolis, Minnesota.

DR. VOEPEL-LEWIS: Terri Voepel-Lewis. I'm an Associate Professor of the School of Nursing in Ann Arbor Michigan at University of Michigan, and an adjunct appointment with Anesthesiology.

DR. LESAR: Timothy Lesar, Patient Care Service Director and Director of Clinical Pharmacy Services at Albany Medical Center in Albany, New York.

DR. HOEHN: Sarah Hoehn, Pediatric Critical Care and Pediatric Palliative Care at University of Chicago.

DR. TURER: Christy Turer. I am a Weight Management Specialist, Med/Peds, and Comorbidity Care. I'm at UT Southwestern in Dallas Texas.

DR. CALLAHAN: David Callahan, Pediatric Neurology, Washington University in St. Louis.

DR. SAYEJ: Wael Sayej, Pediatric Gastroenterologist, Connecticut Children's Medical Center and the University of Connecticut School of Medicine.

DR. HAVENS: Peter Havens, Pediatric Infectious Diseases, Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee.

DR. ANNE: Premchand Anne, Pediatric Cardiology, Ascension St. John Children's Hospital and Wayne State University School of Medicine in Detroit.

MS. BRILL: Marieann Brill. I'm the DFO for this meeting.

DR. WADE: Kelly Wade. I'm the Neonatologist for Children's Hospital of Philadelphia in Pennsylvania, Chair of the PAC.

DR. PATRICK: Stephen Patrick, Neonatologist at Vanderbilt Children's Hospital.

DR. FLICK: Randall Flick, Pediatric Anesthesia and Critical Care at Mayo Clinic.

DR. GRIFFIN: Good morning. Marie Griffin, Internist and Pharmacoepidemiologist at Vanderbilt University.

DR. JONES: Good morning. Bridgette Jones. Pediatric Allergy and Clinical Pharmacology at Children's Mercy in Kansas City.

DR. WILFOND: Good morning. I'm Ben Wilfond. I'm a Pediatric Pulmonologist. I'm also the Division Chief for Bioethics and Palliative Care at Seattle Children's Hospital and University of Washington.

MS. OSTER: I'm Randi Oster. I'm the Consumer Representative and President of Help Me Health.

MS. ROBOTTI: Susan Robotti, founder of MedShadow Foundation and Executive Director of DES Action USA.

MS. CELENTO: Amy Celento, Patient Representative.

DR. PORTMAN: Ron Portman, Pediatric Nephrologist at Novartis Pharmaceuticals, non-voting industry member.

DR. MCCUNE: Susan McCune, Director of the Office of Pediatric Therapeutics in the Office of the Commissioner at the FDA.

DR. HAUSMAN: Ethan Hausman, Pediatrician in CDER's Division of Pediatric and Maternal Health.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the Associate Director for Public Health Initiatives in the Office of Surveillance and Epidemiology in CDER.

DR. GILL: Good morning. This is Rajdeep Gill. I'm the Drug Utilization Analysis Team Leader in the Division of Epidemiology here at the FDA.

DR. MCANINCH: Hi. Jana McAninch. Medical Officer in the Division of Epidemiology, Office of Surveillance and Epidemiology, CDER, FDA.

DR. PATEL: Hi. Chaitali Patel, a Safety Evaluator in the Office of Surveillance

and Epidemiology.

DR. FIELDS: Ellen Fields, Associate Director for Analgesics in the Division of Anesthesia, Analgesia, and Addiction Products in CDER.

DR. LLOYD: Josh Lloyd, Clinical Team Leader in the same division as Dr. Fields.

DR. IBRAHIM: Ibrahim, Drug Utilization Analyst, Division of Epidemiology, CDER, FDA.

DR. GREENE: Good morning. I'm Christina Greene. I am an Epidemiologist in the Division of Epidemiology under the Office of Surveillance and Epidemiology.

DR. BAK: Good morning. My name is Daniel Bak, Drug Utilization Analyst at the Division of Epidemiology at CDER and FDA.

DR. WADE: Again, thank you to everyone for your travels and time today in joining for this discussion. There are often strongly held opinions regarding the topic being discussed at today's meeting. Our goal is that today's meeting will be a fair and open forum for the discussion of the planned topics, ensuring 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.

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, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it along to Marieann Brill, who will read the Conflict of Interest

statement.

CONFLICT OF INTEREST STATEMENT

MS. BRILL: Good morning. The Food and Drug Administration is convening today's meeting of the Pediatric Advisory Committee under the authority of the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act of 2003, the Food and Drug Administration Amendments Act of 2007, the Food and Drug Administration Safety and Innovation Act of 2012, and the Federal Advisory Committee Act.

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

The following information on the status of the Advisory Committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found in 18 USC Section 208, is being provided to participants at this 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 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government 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 government 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 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties, and primary employment.

Today's agenda includes pediatric-focused safety review for OxyContin (oxycodone hydrochloride) extended-release tablets as mandated by the Food and Drug Administration Safety and Innovation Act, and to discuss pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies for opioids generally, using Opana IR as an example. This is a particular matters meeting, during which specific matters related to OxyContin and Opana IR 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.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topics at issue.

With respect to FDA's invited Industry Representative, we would like to disclose that Dr. Portman is participating in this meeting as a non-voting Industry Representative, acting on behalf of regulated industry. Dr. Portman's role at this meeting is to represent industry in general and not any particular company. Dr. Portman is employed by Novartis.

In order to provide the expertise required to adequately address the topic covered at today's meeting, Ms. Celento, Dr. Holubkuv, Dr. Jones, Dr. Lesar, Dr. McGough, Dr. Ortiz-Aguayo, Dr. Patrick, Dr. Perrone, Dr. Sleeper, and Dr. Voepel-Lewis will be participating as temporary voting members. Dr. Jones is participating in this meeting as a temporary health care representative and that is a non-voting position. Ms. Celento is participating as a patient family representative, which is a voting position.

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. 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 topics that could be affected by the committee's discussions. Thank you.

DR. WADE: We will now proceed with the opening remarks from Dr. Susan McCune, Director of the Office of Pediatric Therapeutics.

FDA OPENING REMARKS

DR. MCCUNE: Thank you so much, Dr. Wade. Good morning and welcome to the joint meeting of the Pediatric Advisory Committee, or PAC, and the Drug Safety and Risk Management Advisory Committee, or DSaRM. There are three parts to this fall's advisory committee meeting. The first is today's discussion of the pediatric-focused safety review for OxyContin (oxycodone hydrochloride) extended-release tablets as mandated by the Food and Drug Administration Safety and Innovation Act, as well as the discussion of the pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies, or PREA studies, for opioids generally, using Opana IR as an example.

Tomorrow, the committees will discuss a pediatric-focused safety review of neuropsychiatric events with the use of Singulair, or Montelukast. The third part of the committee review involves the safety review of additional CBER, CDER, and CDRH products. As we have done in the past when there are no new safety issues that have been identified in the pediatric-focused safety reviews, we have posted those reviews for comment in the docket. This fall, we have posted four CBER, twenty-two CDER, and five CDRH pediatric-focused

safety reviews. The docket is open for comment until October 7th.

In addition, I am required to report on the PREA noncompliance letters. These are posted on the FDA website. There are two CBER noncompliance letters. None of these are new since I last reported to the committee. There are thirty-one CDER noncompliance letters, and none of these are new since I last reported to the committee.

With respect to today's agenda, we have presentations from Dr. Foster who is representing the AAP, followed by presentations from the Division of Anesthesia, Analgesia, and Addition Products, or DAAAP, in the Office of New Drugs in CDER and in the Office of Surveillance and Epidemiology -- OSE -- in CDER. There will be an open public hearing following lunch. In the afternoon, there will be additional presentations from OSE and DAAAP, followed by committee discussion and votes.

We are very interested in hearing the views of the public and the committee on these issues, and we look forward to the discussion. With that, I will turn the day over to Dr. Wade.

DR. WADE: Thank you, Dr. McCune. Both the Food and Drug Administration and the public believe in the transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants to advise the committee of any financial relationships that they may have with the firms at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the presentation from the American Academy of Pediatrics, Dr. Jennifer Foster, and then the FDA.

AAP PRESENTATION

DR. FOSTER: Hello, everybody. I have no conflict of interest to disclose. I'm Jennifer Foster from Texas Children's Hospital at Baylor College of Medicine. I'm here, as was mentioned, representing the AAP, to discuss prescription opioids in children and the importance of both accurate labeling as well as adequate treatment of pain.

First, a little bit of an introduction about myself. I'm a pediatric oncologist. I'm board certified in clinical pharmacology as well as pediatrics and pediatric hematology oncology. I treat pediatric patients with cancer, with a focus on patients with solid tumors. I also do developmental therapeutics and Phase I trials for pediatric oncology patients. I'm a member of the AAP Committee on Drugs.

Now, to get into our talk. We've identified two groups who are in desperate need of policy. These are, on one hand, the patients who are taking opioids in a harmful manner, and on the other hand are pediatric patients who are enduring severe pain. In order to manage both of these patient populations, we really need a balanced approach that addresses adequately both of these populations.

The first goal would be to stop opioid misuse and harm. A little bit now about the opioid addiction epidemic. In 2013, there were 3 quarter-million people who were treated for non-medical use of prescription pain relievers. Roughly 19 thousand opioid analgesic overdose fatalities occurred in 2014, which is over a five-fold increase since the late 1990s. Seven thousand people were treated daily in emergency departments for problematic opioid use, and about just under 20 percent of emergency department visitors are prescribed opioids at the end

of discharge. Opioid use disorders cost 72 billion dollars in medical costs annually.

As a pediatrician, I now want to focus a little bit about the role of children specifically in the opioid epidemic. Children less than 18 years of age represent a quarter of the U.S. population. The rate of opioid prescriptions in adolescents ranging from 15 to 19 years of age doubled in just over the decade, from 1994 to 2007. Two million Americans greater than the age of 12 either misused or were dependent on opioid pain killers in 2013, and opioid-related illicit drug use in teenagers is also very problematic.

The other side of that balance that we want to take into account is the effective treatment of severe pain. There are certain conditions in pediatrics which has the potential to result in severe or refractory pain. These include but are not limited to post-operative major surgery including spinal surgery and spinal fusions, as well as correction of birth defects, cancer, which is my specialty, sickle cell pain crises, as well as extensive trauma.

I would now like to highlight a case that exemplifies what we do in clinic and the issues that sometimes arise with managing severe pain in our oncologic population. We recently had a patient a few weeks ago who is a 15-year-old with her recurrence of Ewing sarcoma. Her recurrence presented as a T7 compression fracture and she presented to the ER in intractable pain and was admitted to the hospital on a morphine PCA. By the time of discharge, she was successfully converted to oral, long-acting morphine extended-release 30 milligrams BID, as well as a 30-milligram short-acting for breakthrough.

She was sent home with a discharge prescription to cover two weeks of each of the medicines. Unfortunately, the insurance company denied the long-acting formulation. Dad paid out of pocket full price for the 10 pills, which was for this family in particular a very strong financial hardship.

The prior auth was eventually accepted, but unfortunately four days later her pain was significantly worse because of the rate her disease was progressing. In order to adequately

treat her pain, we increased her long-acting to 60 milligrams BID which was double her dose. So, in order to achieve this, she was taking double the amount of medicine that we had prescribed, and therefore ran out of her pain medicines before that two-week supply had ended.

We therefore ordered a new prescription for the 60 milligrams, but insurance denied it because she had already been recently dispensed. We eventually, after multiple petitioning, got insurance to cover these 60 milligram tablets, but then when the family went to the pharmacy to pick it up, the pharmacist refused to dispense the medication when Dad got there because, “she had just received 30 milligrams of tablets less than two weeks prior and they were uncomfortable dispensing more opioids.” This case is obviously on a very specific patient, but this highlights a lot of the issues and challenges that as pediatric oncologists we face on a daily basis in our clinic.

Obviously, as a pediatric oncologist I care a lot about my patients and adequately managing their pain. And we also have to balance this with the other patient population that I mentioned earlier, which are patients that might be misusing or be able to prevent and treat the addiction. We really need a balanced policy to be able to adequately address both of these patient populations. So, what are some of the pieces of solution in policies as well as clinical practice?

As you can see, on top of here, science is, in my mind, what directs all. Science is what’s going to inform our policy and also lead to informing our clinical practice. And by science, what I mean is drug development, drug studies as well as non-drug studies, and these will, in turn, inform our clinical practice in terms of things such as medication labeling, non-opioid alternatives, as well as quality improvement and payment.

A list of sources also need to be addressed. These include but are not limited to such things such as over-prescribers, excessive amounts prescribed, as well as home medicine cabinets. Addiction treatment is also a huge part of the equation, including prevention and

screening, access to levels of treatment, as well as harm reduction. We have to find a need for more effective certain aspects that I would like to now discuss.

We need more effective non-opioid pain management techniques. We've had a lot of success in post-surgical cases. The opioid use in post-surgery has definitely gone down with the use of Ibuprofen and other types of non-opioid modalities. But we also need a good way, once we have this mechanism, in order to disseminate and implement these techniques so that they are easy to carry out. Prescription drug monitoring programs is another area for improvement as well as opioid return and disposal policies and practices, medication-assisted treatment programs, drug abuse prevention education and training as well as abuse-deterrent formulations.

A few years ago -- I'm not sure how many people in the audience are familiar with this article, but -- the AAP produced a clinical report entitled, *Codeine: Time to Say "No."* And what this was, was a clinical report of drug surveillance on codeine in the pediatric population. In this article, what they highlighted was that the codeine, which had been very commonly used both as an antitussive as well as pain control in pediatric population -- in a subpopulation, most notably those with obstructive sleep apnea, they were having severe respiratory depression which led to death in a few of the patients. Because of this post marketing surveillance, practices were able to be changed for opioid prescription in children.

We've all agreed that there is a need for effective pediatric opioid misuse and addiction countermeasures as well. The AAP is working very hard to both promote the use of screening, brief intervention and referral to treatment for adolescence substance use in the primary care setting, as well as to promote published policy recommending medication-assisted treatment for adolescences with opioid use disorders.

AAP is also working to improve treatment for pregnant women using opioids, improve the care for infants born with neonatal abstinence syndrome, improve parental

substance use treatment to help keep children out of foster care and to address long-term impacts of parental substance abuse on children.

The need for effective pediatric or refractory pain treatment options relies on three main fundamentals. The first is research and development, followed by pediatric drug labeling, and finally, post marketing surveillance. I'd like to talk a little bit more now about the research and development in children. Research and development in children is very, very crucial and should be performed for all drugs. This is because children don't operate like small adults. Children have difference in drug absorption, metabolism, elimination, as well as pharmacodynamics. Pharmacodynamic data is lacking in young children and is an area that really needs to be further addressed in order to facilitate pediatric R&D, especially in the pain population.

Pediatric patients also have difference in drug efficacy and different drug adverse reactions compared to their adult counterparts. Other specific issues that pertain to pediatrics are the impact that drugs may have on growth and development in terms of different drugs may change the way a patient grows and develops and may have an impact on the neurocognitive development; as well as, as a patient grows and develops themselves, the way that they metabolize and process the drug could change.

Clinical trial designs, as we all know, in pediatrics are very, very challenging and an area of ongoing address. The evidence of long-term efficacy of opioids for chronic pain in pediatrics is very limited. Part of this is due to the lack of publication of pediatric opioid use in children. A factor of this may be related to the fact of reluctance to publish. Pediatric exclusivity studies typically are completed very, very late in a drug's life cycle as they are not the initial driver of the clinical trial. And economic benefits from pediatric exclusivity typically come from continued marketing protection from sales to adults.

In addition, once additional marketing protection is obtained, sponsors may not

see a publication as a worthwhile investment. So, even though the data exist on the management of pediatric pain, the data does not exist and is not accessible to all in the form of a publication that can guide policy.

A population that I'd also like some time highlighting is our premature babies and neonates. The reason why I want to take some time specifically to highlight this population is, out of all pediatric populations, this group in particular is administered the most amount of drugs that lack convincing data to support their safety and efficacy. This is upwards of 90 percent of drugs that this patient population receives are not approved by the FDA for the prescribed indication.

This patient population also has unique challenges that go along with it, including ethical issues of doing clinical trials; and in this population, concern for long-term neurodevelopmental outcome given their very, very, very young age. They also represent a relatively very small share of the market, which makes clinical trials difficult. And the risk of developing permanent injuries again because of their age being so young.

Given the considerable morbidity and mortality intrinsic to these premature babies and their very, very complex physiology, we definitely need randomized controlled trials, as well as drug superiority studies assessing improved efficacy of one drug over another. We also need to study both short-term and long-term outcomes and make sure that our surveillance studies go at least until school age where deficits might not appear until a child is in the school setting.

I'd now like to talk a little bit about pediatric drug studies and labeling. I want to start by going over the story of OxyContin. This is the extended-release version of oxycodone, and under the BPCA, the FDA issued a pediatric written request to manufacturer to study oxycodone and OxyContin in children, which was reviewed by the FDA Pediatric Review Committee. Safety and pharmacokinetic studies were subsequently performed in pediatric

patients and this resulted in pediatric labeling.

Because of this labeling, pediatricians and physicians received very specific information in order to safely manage pain in this subgroup of patients, which was a minimum daily opioid use of 20 milligrams of oxycodone. And we definitely look forward to the discussions today continuing the practice of oxycodone and labeling in pediatrics.

I'd like to highlight as well now some of the other pediatric labeling of the opioids and where there might be some areas for further changes in labeling and more evidence. For methadone and morphine, for example, the safety and efficacy in patients less than 18 has not been established. The pharmacokinetics of hydromorphone have not been evaluated in children. And fentanyl, the safety and efficacy in children under two years of age yet has not been established.

Post marketing surveillance is another area that can also address the use of opioids in pediatric population. Clinical trials may not detect all possible risks. Especially in pediatrics, clinical trials do not enroll necessarily the same amount of patients that we have the luxury of enrolling in adult clinical trials. Because of this, you might not have a side effect that appears during the clinical trial, but after the drug is released in post marketing. When you treat hundreds or thousands of more and more patients, you might have side effects that are elucidated that were not part of the initial clinical trial portfolio.

The FDA should focus on drug safety over the entirety of a drug's lifetime and have a very specific monitoring plan including scientific data, the patient's perspective, ethical issues in this special population as well as risk benefit analyses. The need for pediatric drug studies and labeling was taken very seriously, fortunately, by Congress in the early 2000s, which resulted in the passing of both the BPCA, the Best Pharmaceuticals for Children Act, as well as PREA, the Pediatric Research Equity Act. To date, over 800 changes have been made under both BPCA and PREA to add new pediatric information to drug labeling.

So, what have we learned from our experience with BPCA and PREA? This has increased the experience as well as the understanding of pediatric clinical trial design, extrapolation, and formulation. Drugs that were previously thought to be safe in children, some of them turned out not to be, whether it be by under or overdosing. And new indications for children have been discovered.

Today, about 50 percent of drugs used to treat children are used off-label, which is a huge improvement from before the initiation of the BPCA and PREA, which was over 80 percent. So, great, great, great strides have been made in this area and continue to be made. Absence of approved FDA labeling can be a barrier to access of therapies for children, especially patients of my population with very rare diseases.

Recently, the AAP put out a policy statement on the use of off-label drugs in children, highlighting the successes of BPCA and PREA and the work that still needs to be done to ensure that the majority of pediatric drug formulations are able to be included underneath the label. The framework for labeling pediatric medication should be based on rigorous studies. Again, science should dictate everything that we do. Efforts to support and expand drug studies in children need to be continued. Pediatric drug labeling should not, however, be looked upon as a solution for problems that labeling does not cause and cannot solve or serve as an excuse not to grapple with the effective solutions to stop addiction epidemic.

Science should dictate the labeling which, in turn, should inform our clinical practices. When there's drugs that are unlabeled, there is a widely varying clinical practice because the data is not as robust and there doesn't exist the clinical practice guidelines in order to inform the practice. With that labeling comes the addition of studies, and the addition of data, and the addition of information that allows both the label to be made as well as safe, effective and standardized practices to be performed.

In conclusion, we need concrete solutions to address the opioid epidemic. We

must also adequately treat patients with severe and refractory pain and make access to these medicines a lot easier for our patients who need these on a daily basis. And in order to achieve this, we really need a balanced policy that's going to achieve both goals and achieve both goals simultaneously. Thank you, everybody.

DR. WADE: Thank you. We will now move on to Dr. Joshua Lloyd. Sorry. We're having a discussion about whether or not we're going to ask individual speakers clarifying questions at the end of each talk or move between a few speakers. I see that we have 15 minutes left in our agenda, so I think we will go ahead and proceed with clarifying questions for the presenter. I'm sorry for that. So Jennifer Foster, if you could come back to the podium. Yeah? Great. This way, we can have clarifying questions to the presenter and still stay on target. I apologize.

We'll now take clarifying questions for the presenter. Please remember to state your name for the record before you speak. And if you can, please direct questions to the specific presenter. As usual, if you could turn up your name card, then I will know who to call on and I will keep a list. So, we'll start with Dr. Sarah Hoehn.

DR. HOEHN: Sarah Hoehn. Thank you for that exhaustive presentation. I really appreciate it. One of the things I wondered if the AAP or if you had an opinion on, looking at the harm reduction strategy with the role of Narcan, and whether or not the American Academy of Pediatrics specifically has any recommendations for the committee about the co-prescription of Narcan for people with long-acting narcotics.

DR. FOSTER: At this time, I believe that there is not an existing policy from the AAP on the co-prescription of Narcan with the opioid prescriptions. But personally, I do think that that is one of the ways that we can potentially mitigate some of the things that we discuss in the presentation.

DR. WADE: Randi.

MS. OSTER: Thank you for your presentation. My question has to go back to your desire for rigorous studies. You might not know this, but I would love for you to take a moment to tell us how you would define a rigorous study in terms of sample size, in terms of confidence rating, and what we should be looking for as we protect our children.

DR. FOSTER: Yeah. That's an excellent, excellent, excellent question. I think one of the things, especially in pediatrics, is you really need to include a wide range of ages. We know that our patients less than 6 months -- years, because of the ontogeny of the way that their liver develops, that they might not metabolize and react to something the same way as an older patient. This is true as a patient ages. So, we really need to have a representation from different age groups to be sure that that is one of the components.

MS. OSTER: I understand. Can you give me also, as you're answering the question, numbers? Is that ten? A hundred? I'd like us to have a sense of the size.

DR. FOSTER: That's an excellent question. A lot, I think, too, also depends on the initial PKs that you're seeing. If you're seeing PKs that you feel are comparable within the different age groups, or comparable to the adult data, then there's an argument that you can use extrapolation from certain populations. If you're seeing discordance with your pharmacokinetics in the younger group on an initial smaller sample that does not correlate with the adults, then you need to expand your N to be able to include more patients.

I do a lot of Phase I and drug development, so we'll enroll 18 patients on our study and make treatment decisions on dose levels based on a smaller N compared to the adult data. It would need to be little bit more robust than that, obviously, because of the nature, where this is not a Phase I, this is an established profile drug. I don't know the statistics offhand to know specifically that number. But my recommendation would be that you'd probably be able to start with a smaller number if you're having correlation with your PKs in adults. If you're seeing discordant data, then you would need to expand into different patient

populations to make sure that you're really adequately understanding both the pharmacokinetics and pharmacodynamics in the different age populations, as well as in combination with other medicines.

A lot of our pediatric patients do have multiple medicines, especially the ones who have severe and refractory pain. Pain medicine is usually not the only medicine that they're on. So, not only how does that specific opioid work in that patient, but how does it work in the setting of the five, ten other medications that they're on as well?

DR. HOEHN: Sarah Hoehn again, I'm sorry. I had another follow-up question. We know from data in adults that there is increasing suicide rates among those with chronic pain, particularly with all these opioid reduction strategies. So, I was wondering, when you talk about your misuse, were you talking about addiction? Or did suicide attempts from opioids -- was that included in the misuse data?

DR. FOSTER: That's a great point. It was more not including the suicide, but that's a great clarification.

DR. VOEPEL-LEWIS: Hi. I'm Terri Voepel-Lewis from the University of Michigan. I have a couple of questions about post marketing surveillance because that seems to be where, because of the difficulties with randomized controlled trials, where we get a lot of our data in pediatrics including the codeine data that you mentioned.

Does the AAP or you have an idea of how post marketing surveillance should proceed? Because a lot of this is based on review of medical records, not mandatory reporting. And in my experience, we see a lot more adverse events that may not be reported. The codeine statements were based on very limited data. So I'm curious what your thoughts are on that.

DR. FOSTER: Yeah. I don't know offhand if the AAP has a specific policy in terms of how to address post marketing surveillance. And I completely agree that it's drastically underreported. So the cases that are reported, we definitely need to take seriously

because we know that's probably just the tip of the iceberg. But it's very, very difficult to data-mine all of these very large health databases in order to extrapolate that data. I know in bioinformatics, there's a lot of growth and development in that world to be able to try to get at this question. But it is very, very challenging to be able to extract that data.

DR. WADE: I had just a couple of questions as well. The Committee on Drugs and the American Academy of Pediatrics often publishes these clinical reports on medications. I'm wondering if the academy or you have any information as to whether or not these clinical reports that are published by the academy affect clinical care?

DR. FOSTER: That's an excellent question. We hope that our clinical reports are being read and utilized by pediatricians. I don't know if there exists a metric, almost like a pre and post, like what the practices were before versus what the practices were after. A lot of the clinical reports kind of do broad things, such as medication labeling. Like, how many mistakes were made in labeling in individual studies, but not necessarily at an individual practice level? Because that's an excellent -- you want to make sure that the information you're disseminating is actually making a change and getting to your audience. So, ways to do that and ensure that are definitely very important.

DR. WADE: We have a couple more minutes so I'm going to just ask another question. Given your background in clinical pharmacology, I wanted to follow up on Randi's question which is about defining rigor and sample size. I think one of the things we're often struck with is the variation in the pharmacokinetics, these really large standard deviations. Is there a way that we could look at the standard deviation, or the variation that's present in a pediatric population, to then use that as a way of guiding our sample size and how much sample size is warranted?

DR. FOSTER: Yes, that's an excellent question as well. I have kind of a cursory view of the pharmacodynamic and pharmacokinetic modeling. I'm not sure if one of

the statisticians in here has a stronger background in the pharmacodynamic modeling. But there's definitely modeling software and systems that you can use that will determine your N based on that variation you have in your PK and your PD.

So, on a smaller sample size, knowing what that variation is can then dictate how large you need your final -- almost like a pilot trial to determine what your final N really needs to be.

DR. WADE: Dr. Sayej.

DR. SAYEJ: Thank you. Wael Sayej from Connecticut Children's Medical Center. I just have a quick simple question. Just for the record, are there any opioids that are approved in pediatrics? Just so that everyone is aware. And if there are any, what kind of studies have actually been done on those studies in pediatrics?

DR. FOSTER: Ninety (90) percent of my life is the use of off-labeled drugs. So I must say that I don't know offhand what officially has a label indication and what officially doesn't. I know a lot of the ones that do have label indications, they'll go down to 8, 9, 10, 11 years old but they don't necessarily include that younger population. I don't know the answer to that question specifically, but it's an excellent point.

DR. LLOYD: Hi, this is Josh Lloyd from the FDA. Actually, my presentation is going to go over some of that information. Not specifically which opioids are approved, but the data that are used to support the pediatric labeling for opioids.

DR. WADE: We'll have one final question. Dr. Turer.

DR. TURER: My question has to do with specifying outcomes in the trials, because I think the outcome that you use really drives the variability. In thinking about some of those studies that we were looking at, there was multiplicity testing, et cetera. But I think a priori, if you select an outcome that is the most important -- and because my area's weight management, I'm going to use when we were studying the low-carb diets and we were worried

about their impact on LDL. The outcome that we used to drive those trials was actually LDL, not weight. It required a higher sample size, but that was really what we needed to get at. So, my question has to do, really, with what are the outcomes in terms of safety versus efficacy? And how would you prioritize one versus the other?

DR. FOSTER: Yeah, that's an excellent question. In my patient population, we are always skewed more towards less as about the safety and more about how the patient is feeling. Especially when you're in the setting of the terminal cancer -- and we have a palliative care physician here as well too -- you want to do something that's going to have minimal side effects, but your main goal is to control that pain. So, I'm a little bit skewed in my view.

Things like patient-reported outcomes. You know, the faces scale for pediatrics -- there's things that are validated in younger patients as well as incorporating the parental view. Patient-reported outcomes of, I want to decrease my score from this to this or have a predefined percent of decrease in terms of what they're able to accomplish. Are they able to go to school even though their pain is still the 6? Those types of things are very, very important in our population.

In terms of safety, obviously, one of the main safety things for opioids are going to be around the respiratory depression. Being that most of these patients are on multi-pharmacy as well, too, you want to make sure that you're not causing hepatotoxicity or renal toxicity or causing a side effect that's going to add another problem to how they're going to feel. With the main goal being that they're accomplishing everything that they want to currently do in their day-to-day life. Whether that be with pain or without, but that they're able to physically do -- whether it's school or they want to go to the Astros game or whatever it is that they want to do, that they're able to do adequately.

DR. TURER: For each of those, what is the variability in those outcomes? How tight are those outcomes?

DR. FOSTER: I don't have the expertise to be able to address that specifically in terms of what tight of range you would need to need. For the patient-reported outcomes, there's definitely been lots of very validated studies and they're being incorporated into all clinical trials going forward so we're going to have a lot more robust data on how they play out into future studies. But I don't know the nuances enough to know exactly what that percentage or what that power is that you need in order to be able to calculate that.

DR. WADE: Thank you very much.

DR. FOSTER: Thank you.

DR. WADE: We'll now move onto our second speaker, Dr. Joshua Lloyd, on pediatric pain and the approach to studying opioid analgesics in the pediatric population.

PEDIATRIC PAIN AND THE APPROACH TO STUDYING OPIOID ANALGESICS IN PEDIATRIC POPULATIONS

DR. LLOYD: Good morning. My name is Joshua Lloyd and I'm a clinical team leader in the Division of Anesthesia, Analgesia, and Addiction Products. In this presentation, I'll be covering pediatric pain and the approach to studying opioid analgesics in pediatric populations. There's some general principles of pediatric drug development within our current regulatory framework that must be understood prior to discussing obtaining pediatric data for opioid analgesics specifically.

It is critically important to study drugs in children, and there is an ethical responsibility to obtain useful data in pediatrics. Children are not simply small adults, but represent a patient population with potentially different needs, dosing metabolisms and treatment requirements. Some of this information was covered by the prior speaker, but there are two main statutes that govern FDA's ability to request and require pediatric data. One is

BPCA; the second is PREA.

BPCA provides for voluntary pediatric assessments under written request, which may include clinical or non-clinical studies. FDA may request pediatric studies for the moiety and not just the claim indication. This is in contrast to PREA, which you'll hear about on the next slide. If the conditions of a written request are met, then this may entitle the sponsor to six additional months of market exclusivity.

PREA, in contrast to BPCA, authorizes FDA to require a pediatric assessment in the claimed indication for a drug product. PREA is triggered by applications for a new indication, new dosage form, new dosing regimen, new route of administration, or new active ingredient. PREA also outlines the criteria in which the requirements may be waived or deferred. Sponsors have to outline their plan for addressing PREA requirements in a pediatric study plan which must be agreed to by the agency by the time the application is submitted.

The division has developed an approach for studying analgesic drugs in pediatrics, and I will cover those principles, including for opioids, in the next few slides.

Pediatric pain management represents an unmet need in that very few analgesics are specifically indicated for use in pediatrics and do not otherwise contain data informing pediatric use, including for opioids, which have a long history of clinical use. Although pediatric studies have been required for a long time now, very few pediatric analgesic studies have been completed. Fortunately, most infants and children are healthy and only experience brief pain episodes. However, some have severely painful and debilitating conditions -- like you heard in the last presentation -- that require adequate pain management. Despite this, most pediatric analgesic use is off-label.

For many years, FDA required an evaluation of efficacy, safety, and pharmacokinetics for all pediatric age groups. However, few studies were conducted or completed due to challenges in study design and enrollment of pediatric patients. Therefore, we

explored alternative methods for obtaining useful pediatric data so the information on the safe and effective use of these drugs, which are already being used off-label, could be included in labeling to adequately inform prescribers on this use.

One example of this approach is the use of extrapolation of efficacy from adult studies to pediatric population. Pediatric legislation allows for extrapolation of efficacy from adults to pediatric populations as long as the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients. Extrapolation is typically based on demonstrating comparable systemic exposures between adults and pediatric populations in pediatric pharmacokinetic studies, conducted in the intended patient population, provided that the criteria in this slide have been met. It's worth noting that safety may not be extrapolated.

If appropriately used, extrapolation of efficacy is a very useful tool that allows pediatric data to be collected more efficiently, particularly given the challenges associated with studying children. Extrapolation allows for smaller studies and fewer numbers of patients. Despite its usefulness, there are limitations to extrapolation. The concept applies when we can use the known facts to draw inferences, predictions, or conclusions about an unknown. If the mechanism is novel, we have limited understanding of how it may act in children. Also, if PK exposures are inconsistent between adults and children, we cannot draw a conclusion on efficacy based on the PK data alone.

Therefore, it becomes useful to evaluate the data related to efficacy in a study, even if it's collected in an open-label fashion, to provide context for any of the findings. As you will hear in my later presentation today, there are instances where systemic exposures have been demonstrated to be comparable between adults and children, but the open-label efficacy data call into question whether the appropriate dose has been identified.

In 2009, FDA convened a public workshop to discuss pediatric analgesic trial design and considerations, including the available science to support extrapolation for analgesic

drug products. This resulted in a publication on the topic of pediatric analgesic trials. After the workshop, we assessed the information discussed and decided how to apply the latest science to the regulatory approach for studying analgesics, including opioids and non-opioids.

Based on this understanding, we determined that efficacy may be extrapolated from adults down to the age of two for opioid analgesics. In the setting of more chronic pain, for example where extended-release opioid analgesics may be used, we have generally waived studies less than 7 due to the limited numbers of patients that require this therapy and are thus available for study. However, even in this age group, we are aware that sponsors of extended-release products continue to encounter significant enrollment challenges.

Basically, for immediate-release opioid products, we require an evaluation of efficacy, safety, and pharmacokinetics in 0 to less than 2. And then, for 2 to less than 17, we require safety and pharmacokinetic data with extrapolation of efficacy from adult studies. The approach is similar in the extended-release products, except that studies are generally waived less than 7.

Now, I'll shift gears for the last part of my talk this morning to an example of more recently approved pediatric labeling for an opioid analgesic product based on data from post-approval pediatric studies, OxyContin.

Most of the analgesic products used to manage pain in children, opioid and non-opioid, do not have pediatric efficacy, safety, or dosing information because they have not been studied in children. The serious public health problems associated with the misuse and abuse of prescription opioid analgesics, and the problems of addiction, overdose and death, must always be kept in mind when discussing opioid analgesics. However, it is critically important to address the medical needs of children, which includes providing clinicians age-appropriate information about the efficacy, safety, and pharmacokinetics of the products they already use in an off-label manner.

OxyContin was studied in pediatric patients to characterize the pharmacokinetics and safety of the product in pediatric patients who require treatment with this type of product. A pediatric indication was approved for OxyContin in August 2015. However, it is worth noting that this approval did not create novel uses for OxyContin in pediatric patients. But instead provided data in patients who require this treatment so that prescribers may be adequately informed.

Specifically, the pediatric indication approved was for use in opioid-tolerant pediatric patients, 11 years of age and older, who are already receiving and tolerate a minimum daily dose of at least 20 milligrams oxycodone orally or its equivalent. As you can imagine, there was a strong negative reaction in the press regarding the approval of OxyContin in pediatric patients. However, there was also positive reactions from some pediatricians and pain specialists as well as the American Academy of Pediatrics, who treat seriously ill children with pain that require an opioid.

However, recognizing that our understanding of the problems with opioid safety has greatly increased over the span of time that these studies and submissions took place, we created novel post marketing requirements to continue to evaluate the safety of the use of OxyContin in the pediatric population who require treatment with an opioid analgesic. We also want to learn about the possible impact of this new labeling.

In conclusion, FDA has worked and continues to work to develop a rational approach to inform prescribers about the safe and effective use of opioids for the treatment of pain in children. The approach to studying opioids in pediatrics has evolved over time to address the need for pediatric data, particularly given that these products are already used off-label in this population. We encourage sponsors to collect data as efficiently as possible to add knowledge about this population to benefit the pediatric health.

I'd like to acknowledge the help from my division and the contribution of

material from those listed here, which was tremendous help in populating this presentation.

Thank you. Marieann, I sent you a slide. I don't know if we can display that.

MS. BRILL: We're working on it.

DR. LLOYD: Okay. I have a slide as a back-up, which shows all the opioids that have pediatric labeling, those that don't, and other analgesics that do not.

DR. WADE: Thank you very much. While we wait for that slide, we'll now take clarifying questions for the presenter. Again, remember to state your name for the record before you speak. If you can, direct your questions to the specific presenter. Dr. Flick, you were waiting at the last question session.

DR. FLICK: Thank you. Randall Flick, Mayo Clinic. I'm going to ask kind of an obvious, dumb question. But why are pediatric studies not performed? I'm curious to hear Dr. Portman's comment on that. I'll tie it into the last presenter as well. The last presentation talked about the industry reluctance to publish; and I'm curious to know why an industry doesn't publish. And are there ways that we can increase the publication rate of these studies?

DR. PORTMAN: To my knowledge, when a pediatric study is done, particularly based on a written request or a PREA requirement or post marketing requirement, we are obligated to publish the primary study. Now, there may be data that has been gathered during the study that is not part of the primary study that may not be published. And usually that data is available to the academic community. Each company handles that differently.

One company I worked for, basically, any of the investigators wanted the database, they were given the database and the company only asked that they see the publication before it was submitted to make sure that there wasn't any proprietary information. Other companies, currently, will answer any questions of the database and will do any analyses asked and then turn that over to the investigators.

So, basically, industry tries to be as transparent as possible when publishing this.

Also, since we do global trials, one must realize that we also have a requirement for a publication from Europe. And since almost all of our studies are global, we have the obligation not only for FDA, but we'll have it for the EMA to publish those as well. So, I believe we do publish this data.

DR. FLICK: Could the previous presenter maybe comment on what seems like a discrepancy between what you identified as a problem and what industry seems to suggest is not?

DR. WADE: Thank you, Dr. Foster. If you could come to a microphone.

DR. PORTMAN: Sorry, I'll just -- in consultation with my FDA colleague, she brings up a good point. Is that the real problem was with failed trials and not getting those published for a number of reasons; one of them being that journals just didn't accept them because they were failed trials. But yeah, that's a very good point.

DR. FOSTER: That's exactly what I was going to say. I didn't mean to imply that was fully on industry; because that's also, I think, on journals need to be a lot more able to accept those negative trials, because the negative trials are just as informative as the positive trials. And if you don't publish the negative trials, then people keep doing those trials because they don't necessarily know what's been done and they don't know what pitfalls that the other trial might have had. But the not publishing of negative trials, I think, causes a ton of redundant work and data that you could possibly extrapolate for other questions that you just don't have access to.

DR. FLICK: So, Dr. Foster, this would seem to be an opportunity, since the AAP, as I recall, has a journal.

DR. FOSTER: Just a small one. Yes.

DR. FLICK: Yeah. And you have some influence in your group there. It would seem an opportunity for industry and AAP to come together, for the benefit of children, to

publish some of these failed trials.

DR. FOSTER: Exactly. This is the huge issue of my area of oncology as well, too. It's like, there will be a failed trial and you can't get it published, but then someone else will want to do that same mechanism, but they don't realize that it's a futile pass. I think that's definitely a goal to work towards.

DR. WADE: Dr. Jones, do you want to follow up?

DR. JONES: Yeah, I just have kind of a clarifying question for Dr. Portman. When you stated that there is a requirement to publish, were you also including publication as entering data into clinicaltrials.gov? Because that is a requirement, actually, to where data has to be entered in clinicaltrials.gov, although it may not make it to a peer review journal.

DR. PORTMAN: Yeah, that's correct. All of the data from the trials have to be in clinicaltrials.gov. So, for researchers, that's good. But we try to make sure that it's put into the peer literature as well for more general access to those people who are just in the field of drug development.

DR. WADE: Okay. I have a list of people with questions. We'll start with Dr. Havens.

DR. HAVENS: Thank you very much. You mentioned the FDA label that exists that includes the statement, the safety and efficacy of OxyContin have been established in pediatric patients ages 11 to 16. And later in the day, we're going to be asked to sort of address this issue for a younger age group. In the backgrounder that we were given, I noticed that, from the efficacy perspective, over half of the patients withdrew from the study that was presented in the backgrounder for lack of efficacy.

Moreover, protocol deviations seem to be frequent from the perspective of lack of vital signs and respiratory evaluation after dosing. So, one question that comes up is, are there established guidelines that allow these kinds of statements to be made in the label, given the

data that were presented in the backgrounder? In terms of withdrawals for non-effect, which was 56 percent in this study that seems to be presented here to us.

DR. LLOYD: This is Josh Lloyd, FDA. I believe that you're referring to the OxyContin label. And the data that were presented in the backgrounder were for Oxymorphone Opana (IR). And we'll have a discussion of that. That does not have any current labeling for pediatrics.

DR. HAVENS: So the data for the OxyContin were different and better than what we were presented here in the backgrounder?

DR. LLOYD: I don't have the OxyContin data on me right now. But they were reviewed, and the determination was made that the indication could be approved from 11 to 16. And if we had seen issues that raised concerns over efficacy, that would have been an issue.

DR. HAVENS: Thank you.

DR. WADE: Terri

DR. VOEPEL-LEWIS: That's a good segue. I have two questions for Dr. Lloyd about study design for the labeling because of issues like this, where I thought it was two-thirds of the Opana group actually dropped out because of lack of efficacy. So, has there been any thought given to, number one, the pharmacogenetics and the pharmacogenetic response to these drugs? Because some of these kids, especially like the two kids in the Opana study who clearly had different metabolism, seemed to be dropped from that data which is of interest.

Then, secondly, because of the difficulty with clinical trials or randomized trials in pediatrics, has there been any thought given to different study designs like the smart adaptive designs, which mimic more clinical practice, which may make it easier to give better labeling information about efficacy and how to manage patients in pain?

DR. FIELDS: Hi. It's Ellen Fields from DAAAP. We have not reached the point where we're doing pharmacogenetics in terms of the response to drugs. But I don't know

if our clin/pharm folks want to say anything. We don't really have any of the pharmacogenetics folks here, but we're not at that point yet. I'll just leave that.

And what was the second question -- oh, the study designs. Yes, we'd be open to discussing any type of alternative study design. I don't want to say we require a certain design; for the efficacy studies in kids less than two, we have been using the immediate rescue design. And that's generally what sponsors are doing. But if they proposed a different design, sure.

DR. VOEPEL-LEWIS: Can I ask just one follow-up question? What's the intention to treat inclusion in the data labeling? Because it seems to me like some of these patients that are dropped or withdrawn due to adverse events, they may not be included in the data. Is that true or not true? Because it's not clear to me when kids are dropped out of studies, whether or not their data is actually included in the labeling. Is there a requirement for that?

DR. LLOYD: Patients that discontinue from the studies, I guess I would say it depends how much pharmacokinetic data they have. I'll defer to our clinical pharmacology colleagues who are going to respond to your pharmacogenetics question. But it depends on how much data are available from a pharmacokinetics standpoint. However, for safety, they're generally all included. Any patient that received at least one dose of medication is included as part of the safety analysis, regardless of their eventual disposition in the study.

DR. XU: Yun Xu. Clinical pharmacology leader supporting the DAAAP division. For pharmacogenomics data, it's not required for all drugs. Generally speaking, if the drug is metabolized by certain enzymes that we know have enzyme polymorphisms such as CYP2D6. In that case, we may ask a sponsor to collect pharmacogenomics data. But for some drugs, if you know the metabolism pathway is often known to have a polymorphisms, in that case, it may not be required depending on how the drug is metabolized.

DR. WADE: Suzanne.

MS. ROBOTTI: Hi. Suzanne Robotti. Several of my questions were asked

already, so I'm kind of recalculating. I am unclear as to what studies could come into the future given that children are not little adults. And extrapolating for efficacy seems to be -- you know, I'm a layperson, it seems to be not particularly good because of all the dropouts and all the adverse effects.

Giving a pain medication that creates significant adverse effects in 66 percent, up to 80 percent of the kids, I'm not sure how much pain you're really relieving. But also, I look back at the 2016 study design pediatric discussion as was linked to in our stuff. And there were several very good study designs that were suggested, kind of off the cuff.

Dr. Ruhah (phonetic) suggested retrospective studies at pediatric centers looking at children who initiate in opioids and tracking their initial starting dose, doing retrospective studies, looking at whether they had respiratory depression following it, naloxone reversal. Dr. Kibey (phonetic) outlined another research technique creating a chart the clinicians all over the country could fill in, giving more detail.

Was that followed up on? Are we going to be seeing those studies or anything like that? Is there open, live, active information being gathered now with all these children getting the drug? Why don't we see what it's doing to them live?

DR. LLOYD: So, is your question have we received information on novel study designs that were discussed --

MS. ROBOTTI: Yes, my understanding is that the FDA is involved in the study designs and discussion of study designs, so you have an idea of what kind of studies are out there in development.

DR. LLOYD: This is Josh Lloyd, FDA. As Dr. Fields noted, we are open to novel study designs and approaches, particularly for collecting pediatric data where -- as I described, there is significant challenges in collecting those data. We work with sponsors on their pediatric study designs in the context of their pediatric program, and to date I have not

seen any of the novel designs that you're referencing.

DR. WADE: Dr. Perrone.

DR. PERRONE: Yes, thank you. You have to take this from the perspective that I'm an emergency medicine physician practicing addiction medicine in the adult and emergency department, next to a children's hospital. So I'm well aware that exposure to opioids in childhood does trigger that eventual development of opioid use disorder in a fraction of patients. But that is my perspective.

So, for slide 19, when we talked about some of these post marketing requirements, long-term we're looking at misuse. But are we looking at the development of opioid use disorder after exposure to these medications, which may be several years later or gradual? Sort of, that goes hand-in-hand with the -- you know, I'm not aware of what the overall survival rate is of childhood cancer, but what we're seeing in adults is, in fact, that obviously the survival rate is tremendously higher than it was. Our viewpoint of treatment with opioids in a cancer population previously might not have been looking at the future of that patient in terms of being off opioids. So, we certainly see patients with cancer who also have developed opioid use disorder.

Overall, I would say that -- I'm not sure the mortality of childhood cancer, but the mortality of OUD, or opioid use disorder is tremendously high. So, looking at the development of that disorder, in patients who are exposed to OxyContin, thinking back what we know about adults who were exposed to OxyContin, that long-term pharmacokinetics really influenced the way patients developed their dependence and ultimate misuse. So, I think that should be factored into data that we collect.

DR. STAFFA: This is Judy Staffa. One of our presentations later on today will be talking about reviewing the literature in that area to bring the committees up to speed on what's known about that.

DR. PERRONE: In that Slide 19, the misuse, are they tracking the development of opioid use disorder? Misuse is sort of the first stage but would need a longer-term surveillance for each patient who gets exposed.

DR. STAFFA: This is Judy Staffa again. I don't believe in the actual PMR studies that there's longitudinal tracking. There are tracking reports of outcomes specific to OxyContin.

DR. PERRONE: Thank you.

DR. WADE: Randi.

MS. OSTER: Randi Oster, consumer representative. One of the observations I've had in the studies is that when they make a conclusion, the conclusion about pain reduction tends to be as subjective as asking a patient, "What's your pain?" So, the studies will refer to that we ask, on a scale of 1 to 10, what is your pain? And then the study conclusion, for example, says overall, it appears that patients in the active treatment groups had less pain.

So, one question I'd like you to comment on is, why can't we quantify pain if we're looking at this to use? Why is just less pain acceptable? And the reason that I want to emphasize this is -- I will take one study, for example, and it's the study for when they were comparing it with morphine. I can give you the number later. But in this case, 55 percent of the people in this study had adverse reactions that -- most probably nausea and these other things -- were causing them pain. So my question specifically is, how do we design these studies so that we really know if pain is being reduced? And why is it acceptable not to have some quantifiable results?

DR. FIELDS: Hi. It's Ellen Fields from DAAAP. I'm not sure exactly which study you're talking about, but there's two types of studies that are done. There's controlled studies that are double-blind; and in those studies there's a primary endpoint of pain and we would quantify the pain scores and use statistics to see if they're statistically significantly

different between the two study groups.

In the kids that are over 2, we do open-label studies. We may collect pain data, but it's not versus a control. So it could be supportive of seeing some pain reduction, but we rely primarily on the pharmacokinetics and the exposure in children being similar to the exposure in adults. That may be what you're referring to in an open-label study design. Certainly, we would look at the change in pain scores. But because it's not a controlled study, it doesn't have as much strength in terms of determining efficacy as a double-blind study would. Does that answer your question?

MS. OSTER: It does. I just would like, for the record, if you could give me an example in the studies that we've been given. I did not see in one case any study where it gave a number for what the pain reduction was. I can go through the studies, but we don't have to do that here.

DR. FIELDS: Yeah. I mean, I'd have to look into the backgrounder and see what we have.

MS. OSTER: All right. I'd appreciate if you could show us one.

DR. FIELDS: It may be that we -- are they all open-label studies in the backgrounder?

DR. LLOYD: Yeah. For the discussion later this afternoon, for Opana Oxymorphone immediate-release, all of the studies are open-label studies. Because the general approach in the 2 years of age and older group is PK and safety with extrapolation of efficacy from adults.

DR. FIELDS: So, there are no double-blind controlled studies for efficacy in children 2 years to less than 17, because we're relying on the pharmacokinetics to support the approval.

MS. OSTER: Okay. Then the open question is, how much pain is actually being

reduced? I just would like to leave that out there.

DR. FIELDS: We have the data.

DR. WADE: Thank you, Randi. I think this afternoon we will stay on the topic of the OxyContin study.

MS. OSTER: No, I brought it up because it's the studying of opioid analgesics, so I want to understand how we study it in terms of actual pain reduction. That's the reason for the question at this time.

DR. FIELDS: Hi, it's Ellen Fields again. Again, these are open-label studies in children greater than 2 years of age. So, we do obtain pain data. And I think in the Opana example, there wasn't a decrease in -- I don't want to say something that's not right. But they're open-label data. So, we rely on the pharmacokinetics, the exposure being similar in adults and children, and as long as the pain data trends in the right direction, given that it's open-label, that is sufficient to support whether the drug is analgesic in these patients.

We know that these drugs are analgesics. It's already been shown in adults. So, we can extrapolate the efficacy from adults and obtain safety and PK data in the children. That's how the studies are done over the age of 2.

DR. WADE: As it seems like a lot of our questions are quite broad this morning, I think, for the essence of time, we should move on to the next speaker. I have all four of these individuals over here with questions, but I wonder if we can move onto the next speaker and then continue in this realm of questioning given the global nature of the topic. I would now welcome Dr. Ibrahim.

PEDIATRIC UTILIZATION PATTERNS OF OPIOID ANALGESICS

DR. IBRAHIM: Good morning. My name is Ibrahim Ibrahim. I'm a drug

utilization analyst from the Division of Epidemiology in the Office of Surveillance and Epidemiology. I will be presenting data about the pediatric drug utilization patterns for non-injectable opioid analgesics from 2009 through 2018 to provide context for today's discussion.

Here is the outline of my presentation. I will begin with the sales distribution data of opioid analgesics, followed by the prescription utilization patterns in pediatric patients from the outpatient retail pharmacy settings, our findings from the diagnoses associated with the use of opioid analgesics in the pediatric patients, limitations of our analysis, and conclude with a summary of our findings.

This slide shows the opioid analgesics included in our analysis. The analysis focused on non-injectable opioid analgesics, mainly dispensed in the outpatient retail pharmacy setting, excluding injectable formulations of opioid analgesics, opioid-containing medication-assisted therapy products and opioid-containing cough and cold products.

The settings of care where opioid analgesics were primarily utilized in 2018 was determined based on the sales volume for manufacturers using the IQVIA National Sales Perspectives Database. Opioid analgesics were distributed primarily to the retail pharmacy setting in 2018, therefore, we focus our analysis on the outpatient retail pharmacy setting.

To conduct these analyses, we used a variety of proprietary databases available to the agency. For prescription utilization data, we used databases that measured the dispensing of prescriptions from outpatient retail pharmacies to patients based on transactions from a robust sample of retail pharmacies. Data are projected to provide national estimates of drug utilization.

This graph shows the estimated number of all patients who received opioid analgesics prescriptions from U.S. outpatient retail pharmacies from 2009 through 2018. Of the estimated 50 million patients of all ages in 2018, pediatric patients accounted for 3.5 percent, a decrease from 6.5 percent of total use in 2009. Of note, pediatric patients 0 to 17 years old are inclusive of all patients from birth up to the day before their 18th birthday.

This graph displays the pediatric outpatient use of opioid analgesics from 2009 to 2018. The gray bars represent the total number of pediatric patients dispensed opioid analgesics, and the lines show the top five most frequently dispensed opioid analgesics. Pediatric utilization of opioid analgesics decreased from an estimated 4.2 million patients in 2009, to 1.8 million patients in 2018. During the examined time period, use of opioid analgesics decreased in pediatric patients across the majority of opioid analgesics products.

Approximately half of the pediatric patients received combination codeine-acetaminophen in 2009. But as its use declined, as you can see here, combination hydrocodone-acetaminophen was the most utilized opioid analgesic since 2011. However, use of single-ingredient oxycodone increased from an estimated 31 thousand patients to 150 thousand patients, as shown by the blue line near the x-axis. This pattern was observed in all pediatric age groups. Later this afternoon, Dr. Daniel Bak will present the drug use patterns of oxycodone. I will now present the utilization patterns by more granular pediatric age groups.

This graph presents similar data for patients less than 2 years of age. Note the y-axis is in the thousands. Although not shown here, patients less than 2 years of age accounted for 2 percent of the total pediatric patients receiving opioid analgesics in 2018. Patient use appears to have decreased by approximately 70 percent from 2009 to 2018. In 2009, the majority of patients in this age group received codeine-acetaminophen. But as its use declined, hydrocodone-acetaminophen became the most frequently dispensed opioid analgesic in recent years. Codeine-acetaminophen use has decreased by 98 percent since 2009.

This graph shows data for pediatric patients 2 to 11 years old. Patients 2 to 11 years old accounted for an estimated 26 percent of the total pediatric patients receiving opioid analgesics in 2018. Similar to the previous slides, the number of patients decreased by approximately 73 percent from 2009 to 2018. Patients 12 to 17 years old accounted for the majority of pediatric use of opioid analgesics at an estimated 72 percent of all pediatric patients

in 2018.

This subgroup of patients showed a less steep decline than the other pediatric age groups, with an estimated 47 percent fewer patients in 2018 compared to 2009. Unlike the trends seen in the other age groups, hydrocodone-acetaminophen products were the most utilized opioid analgesics in this age group throughout the study period, followed by combination codeine-acetaminophen. However, use of both opioids appears to have declined.

Of the estimated 168 million total prescriptions dispensed in 2018, pediatric patients accounted for 1.2 percent, or 2.1 million dispensed prescriptions. Of the prescriptions dispensed to patients less than 2 years old, the top three prescribing specialties were urology, followed by surgical specialties such as general surgery, orthopedic surgery, critical surgery, and lastly, the combined specialties of nurse practitioners and physician assistants, including those practicing in primary care or specialized fields. For patients 2 to 11 years old, prescriptions were primarily to obtain by otolaryngology, followed by surgical specialties and dentistry. For patients 12 to 17 years of age, prescriptions were written by surgical specialties, followed by dentistry and the combined specialties of nurse practitioners and physician assistants.

We obtained diagnosis data associated with the use of opioid analgesics from a database that captures monthly surveys from a sample of 3,200 office-based physicians with 115 pain specialists, reporting on patient activity during one day per month. These data are nationally projected and provide an insight into the prescriber's intent. These data may not be necessarily linked to a dispensed prescription, but rather indicate that a drug was mentioned during an office visit. Of note, dental offices are not a part of this sample. Therefore, dental diagnoses are not captured in this database.

This slide shows the diagnoses associated with opioid analgesics for pediatric patients stratified by the different age groups. For patients less than 2 years old, fractures and

injuries and other and unspecified soft tissue disorders were the only reported ICD-10 codes in 2018. For patients 2 to 11 years old, fractures and injuries and inguinal hernia were the top reported diagnoses in 2018. Fractures and injuries, and scoliosis were the top reported diagnosis for patients 12 to 17 years old in 2018.

This data has some limitations. Only outpatient utilization was analyzed. Therefore, no inpatient or mail order data were included in the prescription analysis. The diagnoses data were not necessarily linked to prescriptions, rather that a drug was mentioned in association with a diagnosis during a patient visit to an office-based physician.

The diagnosis data were derived from surveys of office-based physicians and does not capture use of opioids for dental indications. Also, it may not be reflective of prescribing patterns for physicians who practice in other clinical settings, such as hospice or inpatient centers, emergency departments, or surgical centers and does not include mid-level practitioners.

In summary, in the outpatient setting, 1.8 million pediatric patients utilized opioid analgesics in 2018, a 59 percent decline in use from 2009. The top five most utilized opioid analgesics are shown here. The decrease in use was largely driven by the decrease in pediatric use of combination codeine-acetaminophen and hydrocodone-acetaminophen. The only top five opioid analgesic that appeared to increase in use during the examined period was single-ingredient oxycodone IR, although use remains relatively low.

Surgical specialists, primary care physicians, and dentists were the top prescribing specialties in 2018. According to the office-based physician surveys, opioid analgesics were mainly mentioned to be used for the management of pain associated with acute conditions -- mainly fractures, injuries and inguinal hernia in pediatric patients. However, dental use was not captured. Thank you.

DR. WADE: Thank you. We have some time remaining before our break this

morning to continue with our clarifying questions for the presenters. Again, I'll remind you to remember to state your name for the record before you speak. And especially now that we have had three presentations, if you can please direct your questions to a specific presenter as you see fit.

We'll continue with the questions that were already slated. We'll start with Dr. Sleeper.

DR. SLEEPER: Thank you. I just wanted to make a couple statistical comments that hopefully are a partial response to some of the questions that were raised for the first two presentations in case they're helpful. They're on about three or four different topics.

The first had to do with the aspect of discontinued patients in studies, and people wondered how those data are or are not used. Typically, the ideal is that data are collected, even after someone's discontinued from a drug, that you're still able to collect their data for the full study time period, so they're withdrawn from perhaps the testing agent but not from the entire study. If that's not possible to include those data or intention to treat analysis, then ideally a statistical analysis plan would have a sensitivity analysis where people would use a best or worst-case rating or score or whatever the measurement is; and see if the original findings based on the smaller data set are robust to those changes by using a best or worst-case scenario substitution for the discontinued patients.

The second comment was about publication bias and the concern about having a lack of negative studies in the literature. I just wanted to comment that there actually are -- publication bias is sort of a form of what's called p-hacking, that we're not really seeing all the information that's out there or getting a misconstrued view of what that is. And there actually are now journals, more in the social science literature, but that are actually advocating applying for -- notifying the journal of a particular trial, and the journal agrees to publish the trial in advance of having the trial completed, irrespective of whether it becomes positive or negative

results. That's actually a really great step in the right direction against publication bias. It'll be nice to see further into other fields.

Last, my comments were just about study design in terms of endpoints and variation and people are asking how many is enough? That's a really broad question that any statistician would never tell you the answer for without having any specifics. But it is true that the variance of the measurement is directly related to the required sample size; so ideally, you'd want to design a study that has a lower coefficient of variations.

So, for instance, in some of the studies I was looking at in preparation for this meeting, some of the patient reported outcomes had a coefficient of variation that was half that of some of the supplemental opioid usage. So, you might want to design a trial that includes those kinds of outcomes, or possibly have composite outcomes which are combinations that could be rank, or score based. They can also really decrease the required sample size from maybe later phase study, from hundreds down to dozens even, depending on what the outcomes are.

And last there was a comment about adaptive designs. I think there definitely are a lot of adaptive design approaches out there now that I think -- my experience is the FDA has been receptive to some of those. Those include things such as evaluating the variance that you are observing in a study part way through the study, which does not negatively impact some of the statistical properties of the final result.

So, that can allow you to actually increase or decrease the size of your study part way through, depending on the variation you're seeing; which in terms of the pediatric field could mean that a study could be done with fewer patients and we could get quicker results. Or it could mean that you've increased it appropriately and actually get results that can give you an answer to the question that's being raised.

So that's one type of adaptive design. Another is looking at different dose groups

and combining them partway through or dropping an arm if there's no difference being seen in certain groups. That's also another way to have more rigorous studies that can answer the questions of interest. Thank you.

DR. WADE: Thank you for those comments. Dr. Turer?

DR. TURER: Thank you. Christy Turer. I recall at a prior PAC meeting, we had discussed the importance of tolerance developing, really in the neonatal units. So, I think it has important applications both for -- you know, we're looking at the numbers of outpatient prescriptions, but frequently those are dispensed at least, like in oncology, after an inpatient stay. And one of the questions, in thinking about the mechanisms of tolerance, you've got opioid receptor down regulation, you've got some allostatic changes to downstream circuitry. We know this happens in the neonates. We have less data as children age, and it's not clear to me whether it's a lack of it happening versus a lack of data. When kids are in an ICU, it's kind of like you got petri dishes in the hospital so that you're able to study that.

So, I do think that we need data on inpatient use and that the preceding inpatient use is factored into any outpatient trials looking at the impact on pain because there may be tolerance that develops. That really, I think, just is incredibly important. And I don't know that we have the answer. I don't know even who to direct those questions to, but I think we need to appreciate those effects.

DR. WADE: Great. Dr. Patrick?

DR. PATRICK: Stephen Patrick from Vanderbilt. My question is for Dr. Lloyd. And it really is just around what sort of standards and requirements are given to manufacturers in terms of the study quality? I think one of the questions that we all have, realizing that some of these things are open-label, is when we see signal around efficacy or around safety that are concerning, we're sort of grappling with what deserves to be on the label, what's the bar to be on the label, and understanding that -- certainly, in my current practice setting as a

neonatologist, most things are off-label. So, more data would be helpful.

But worrying about what is the bar in terms of the data quality that reaches the ability to inform providers? Part of that, to me, begins with, what are the standards that are set forth for manufacturers as they begin to do some of these, even open-label studies?

DR. LLOYD: This is Josh Lloyd, FDA. So we look at all of the data on a case-by-case basis. We look at safety and efficacy in the pediatric population. And the efficacy in the age group that we're going to be discussing later today, the greater than 2 age group, is primarily based on the pharmacokinetic data, based on extrapolation of efficacy from adults. That was based on the information that came out of the 2009 public workshop, which included a variety of pain specialists and scientific experts. But that being said, we also look at the open-label efficacy data in those studies to make sure that everything looks like it's going in the right direction.

So, some of the data that we look at in the open-label studies regarding efficacy are the pain scores, obviously, rescue analgesic medication use. We also look at disposition. We talked about dropouts due to lack of efficacy. And one of our concerns about the example that we're going to talk about later today, is that the company did demonstrate comparable exposures. However, some of the open-label data called into question whether or not the right doses were being administered.

So, those efficacy data are then used -- if we're able to extrapolate efficacy and all of the open-label efficacy data sort of support that conclusion, then we might consider an indication in the pediatric population or subpopulations. We also look at safety. Safety data are not extrapolated. So we use the data from the clinical studies to establish the safety of the product in the pediatric population.

So, even if we're extrapolating efficacy based on the pharmacokinetic data, that doesn't obviate any safety findings that are identified in the trial. Those are considered fully.

And then that would also go into the indication. And if the data don't rise to the level of an indication, we have the ability to include some of the pediatric data in other sections of the label, like Section 8, which describes the pediatric use, which would describe the experience that was documented in the clinical study.

DR. PATRICK: Just a quick follow-up, if I may. I think the question -- are there a priori standards of this is the approach you should take to manufacturers? In terms of, this is the threshold we'd like to see for this, that or the other thing in terms of just even written communication. That's what I'm curious about, in terms of. Or is it case-by-case based upon kind of the broad strokes of things?

DR. LLOYD: Josh Lloyd, FDA. The a priori sort of approach for establishing efficacy in this population would be to have enough data to describe the pharmacokinetics in relation to adults. And then, regarding safety, it really depends on what we see in the clinical studies. We often, ahead of time -- and it really depends on the product -- will describe a minimum safety database that we require for certain products, how many patients that need to be exposed. Because that, again, would go into the indication. In the case of OxyContin, there weren't sufficient patients less than the 11 years of age. So, that's reflected in the indication.

So, yes, we do, in cases, identify ahead of time what the minimum safety database requirements are. We also ask the sponsors to look at literature documenting the safety of the product in pediatrics. And we review all of that information as part of the supplement to the NDA to make an ultimate determination on the safety of the product in the pediatric population.

MS. OSTER: This is Randi Oster. Building on this conversation and going back to the challenge that you brought up and talking about the labeling, I just want to take a moment to talk about the numbers because that's what your question was. What is the direction? What should the manufacturers be told that they should be looking at? So, as a consumer, I would love it to be a 95 percent confidence level. Right? That I know that, within plus or minus 3

percent, the sample size for that is 1,066.

So, I want to then take a moment to just look at some of the numbers just so we have an understanding. When we have a sample size of 13 and there's just one defect, one adverse event, that's a 2.9 sigma and that translates into a million people to 76 thousand people will have that same adverse effect. So, your question that you're bringing up is, when we're going to be addressing labeling and what do we have to say? How do we clearly document the sample size and what we know with these numbers to be the risks of that drug? We do know size data -- that's just math -- and we do have the information here. So, the question is then how later are we going to be advising, with these sample sizes, the results?

DR. PATRICK: I just think that one of the tensions is that -- particularly neonatology and most pediatric -- if we wait for that study of multiple thousands, we're not going to get there. So, this tension of, what is the threshold with the limited sample, how can we use novel study designs and modeling, and what is the sort of data quality that goes into that specific modeling and what are the standards there? That's kind of my curiosity in terms of -- I think we would all like large, multicentered trials, but it's difficult to pull off.

MS. OSTER: Right. And the question on the table is the labeling. So, we're not saying that we have to change the sample size; we have to be clear with what the sample size is and what the results are.

DR. PATRICK: Yes. Thank you.

DR. WADE: Great. So, let's go down this row here. I think, Christy, we handled your question? Okay. Let's see if we can get through these so we can go for a break. Sarah?

DR. HOEHN: Sarah Hoehn, University of Chicago, palliative care. I have two quick comments in follow-up of what we were talking about with study design from what Randi said. Certainly, in that chronic pain population, we're moving away from pain scores and really

focusing on function. Can you get out of bed and walk to the door? Can you sit up and play on your phone and eat your meal? We're really, in the older population, trying to focus on function, but it's a hard thing to quantify.

And then the other thing in terms of studies, it's going to be almost impossible to do a placebo-control trial in pediatrics for pain. That's true if you're looking at cancer pain or sickle cell or anything else. So, I think we just have to be mindful of that, that we still have an obligation to treat them while trying to identify the pharmacokinetics and everything else.

Then my third is a clarifying question for Dr. Ibrahim; which is, I was wondering if he has any prescription data on the rates currently of Narcan prescriptions -- in particular that nasal spray. If we have any data on what the current prescription rates are in the utilization today? So, that's a question.

DR. IBRAHIM: Not currently, no. That wasn't part of the analysis that we did for this PAC.

DR. STAFFA: This is Judy Staffa. We actually had an advisory committee in December where we presented prescription data on Narcan, which is only a piece of what's out there. Because, as you know, there's a lot of different community-level distribution programs. But I'm sure we can get you the link to that meeting, and the presentations, so you can take a look and see what we presented at that meeting.

DR. HOEHN: Even if there's like a two-minute summary, I think it might be helpful for us this afternoon. If there's any -- like one paragraph or any summary; I think it just might be helpful framing some of the conversation.

DR. STAFFA: This is Judy again. We can look and see if there's anything relative to pediatric use or prescriptions.

DR. WADE: Great. Dr. Meisel?

DR. MEISEL: Thank you. Steve Meisel of Fairview in Minneapolis. Two brief

questions for Dr. Ibrahim. The data you presented are the number of patients with a prescription. Do you have data, or can you get data on the number of tablets per prescription or the number of morphine milligram equivalents that have been utilized over the course of time? Because the number of prescriptions is one thing. The bulk is a very different dynamic and a very different measure.

DR. IBRAHIM: Yes, I believe we can, but it is not something that we looked into for this PAC presentation. But we'll be happy to look into it and get back with the members here, maybe in the near future. I believe it is something that we can do.

DR. MEISEL: Okay. And then this relating question, the number of patients with a prescription has gone down, as you presented, by 70, 75 percent in some cases. Do we know why? Has there been a comparable increase in prescriptions for other analgesics such as NSAIDs? I know some of them are over the counter and would be harder to quantify. But is it a reduction in the number of patients who are prescribed anything for pain? Or is it a substitute with something that you otherwise didn't quantify, such as NSAID or something else?

DR. IBRAHIM: Our analysis did not look at NSAIDs. But we do know that the reduction in use was driven largely by the reduction in use of hydrocodone-acetaminophen and codeine-acetaminophen. The codeine, although that might not be the only contributing factor, but the agency has released a couple of box warnings and contraindications for codeine-acetaminophen, and that might have driven down the use in these sets of patients. But we haven't looked at NSAIDs.

DR. MEISEL: Right. So, we don't really know what's driving that? If it's just reduction in prescribing opioids or whether it's a shift in clinical patterns that we're not prescribing analgesics as often as we were. We don't really have a feel for that?

DR. STAFFA: This is Judy Staffa. You're right, we don't. The data do not show the reason behind that. But if folks here -- we'd be interested in hearing clinical

experience whether folks have thoughts on that.

DR. WADE: So I have Angela and Richard up next for questions, but we are due for a break. So let's take a 15-minute break, come back at 11:05 and we will complete this round of questioning before we move onto our next presentation.

[BREAK]

PRESCRIPTION OPIOID ABUSE AND RELATED OUTCOMES IN THE PEDIATRIC POPULATION

DR. WADE: So I know we have two more questions at hand and from those Angela and Howard I wonder if you feel like the questions are on target right now, or if we can hold them until after the last presentation before lunch? Thank you for that flexibility. We will move on now to Dr. Christina Greene to talk about prescription opioid abuse and related outcomes in the pediatric population.

DR. GREENE: Good morning. My name is Christina Greene. I am an epidemiologist at the FDA in the Office of Surveillance and Epidemiology. And I will be discussing prescription opioid abuse and related adverse outcomes in the pediatric population. For regulatory questions that involve drugs with abuse potential, such as opioids, FDA considers the public health risks associated with misuse and abuse of these drugs in the community. The objective of this presentation is to review the available epidemiologic data to inform considerations of the public health risks associated with pediatric opioid use.

First, I will define what is considered misuse and abuse by the FDA. Then, I will describe the epidemiology of pediatric opioid misuse and abuse using various data sources. I will then review the current literature on the risk of misuse, abuse and substance use disorder

following pediatric prescription opioid therapy. I will then discuss the limitations of the data and literature and conclude with an overall summary.

The FDA defines misuse as intentional use for therapeutic purposes of a drug in a way other than prescribed or for whom it was not prescribed. This differs from the regulatory definition of abuse, which is intentional nontherapeutic use of a drug to achieve its desirable psychological or physiological effects. It is important to note however, the terminology varies across different data sources.

I will now describe the epidemiology of pediatric opioid misuse and abuse. I will discuss the prevalence of prescription opioid misuse and abuse in adolescents using two sources: the National Survey of Drug Use and Health, or NSDUH, and the Monitoring the Future survey, a nationally representative school-based survey of adolescent drug use behavior. I will then present data on prescription opioid-related emergency department visits using the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance, or NEISS-CADES. Next, I will describe pediatric prescription opioid exposure calls to U.S. Poison Control Centers in the National Poison Data System. And finally, I will present data on drug overdose deaths involving prescription opioids using the National Vital Statistics multiple cause of death mortality data.

This figure shows the prevalence of past year prescription opioid misuse and abuse among adolescents ages 12 to 17, for 2015 through 2018, first overall on the far left and then for individual opioids. These percentages have been declining over the past four years from 3.9 percent in 2015 to 2.8 percent in 2018 for misuse or abuse of any prescription opioids. The drugs that are most often misused by adolescents are hydrocodone, oxycodone, codeine, and tramadol.

This graph shows the percent of high school seniors who've reported past year misuse or abuse of prescription opioids in the Monitoring the Future survey from 2010 to 2018.

This percent has been steadily declining from 8.7 percent in 2011, to 3.4 percent in 2018.

This table shows 2018 NSDUH data describing where adolescents reported getting the prescription opioid they most recently misused or abused. Almost half reported acquiring the medications from friends or relatives, most of which were given for free. However, over a third of adolescents reported that they got the drugs from their personal prescription.

This table describes the source of misuse or abused prescription opioids among high school seniors in the Monitoring the Future survey. The categories presented here are not mutually exclusive, as respondents may have indicated various sources. Similar to NSDUH, the most common source of drugs was from a friend or relative, usually given for free. Here, nearly a third of respondents reported their own prescription as the source.

This table shows the national estimated annual number and rate of opioid-related ED visits due to nonmedical use and self-harm of prescription opioids in adolescent and adult age groups. In 2016 and 2017, there were an estimated two to three thousand visits annually in 12 to 17-year-olds for both nonmedical use and self-harm involving prescription opioids with the estimated number of self-harm visits being slightly higher. The rate of visits due to prescription opioid nonmedical use was much higher among adults than adolescents. However, the rate of visits due to self-harm involving prescription opioids was not significantly different between adolescents and adults.

To provide some context, this table shows the estimated numbers and rates of ED visits due to adverse events involving therapeutic use of prescription opioids. These visits include events such as allergic reactions, medication errors, and unsupervised ingestions by children. There were an estimated 4,600 annual ED visits in the United States due to therapeutic prescription opioid use in children ages 11 and under. There were approximately 1,500 ED visits due to therapeutic prescription opioid use in adolescents between the ages of 12

and 17. The rate of adverse events following therapeutic use was higher in younger children than in adolescents, yet still lower than adults.

This table shows findings from a 2017 publication that examined U.S. Poison Control calls for prescription opioid exposures in individuals 19 years of age or younger. In children ages 5 and under, most calls were due to general unintentional exposures. Most exposures in children between 6 and 12 were unintentional and due to therapeutic error, such as accidentally taking too strong a dose of prescribed medication. However, in teenagers, over 70 percent of exposures were due to intentional reasons, with nearly half of these calls being suspected suicides and most of the remainder being due to misuse or abuse of prescription opioids. The source of the medication involved in these exposures is not documented.

The rate of prescription opioid exposure calls increased from 2000 to 2009, and then declined from 2009 until 2015 in all pediatric age groups. This trend was not consistent across all reasons for exposure, however, as the rate of suspected suicides involving prescription opioids in teens increased by 52.7 percent from 2000 to 2015.

This figure depicts medical outcomes of calls involving prescription opioid exposure. Most prescription opioid exposure calls in children 12 and younger resulted in no clinical effect. Teenagers, however, were more likely to have an exposure resulting in symptoms often needing medical monitoring and treatment. The few deaths show up as a thin line at the top of each bar. National mortality data showed that, in 2017, there were 50 drug overdose deaths due to prescription opioids in individuals 14 and younger, and approximately 1,000 in those aged 15 to 24. The rate in 15 to 24-year-olds decreased 7.7 percent from the corresponding rate in 2016.

I will now go into a brief review of the literature investigating the association between pediatric opioid use and future risk of misuse, abuse, and substance use disorders. We identified studies that examined the association between medical use of prescription opioids and

future misuse, abuse, or substance use disorder symptoms. Compared to adolescents who did not use any opioids, adolescents who used prescription opioids only as medically directed were more likely to engage in opioid misuse or abuse in early adulthood and in early midlife. These estimates adjusted for sex, race and ethnicity, geographical location, parental education, and history of other substance use. Among students that had a history of both medical use and misuse of prescription opioids, medical use most often preceded the initiation of misuse.

This table shows the results of a recently published study that examined the risk of substance use disorder symptoms at age 35 associated with medical use or misuse/abuse of prescription opioids by the end of high school. The outcome was measured using DSM-5 Diagnostic Criteria for Substance Use Disorder, which in its more severe form corresponds to the concept of addiction.

Medical use only without misuse or abuse as well as medical use that preceded nonmedical use were not associated with self-reported symptoms of substance use disorder at age 35. However, medical use after misuse or abuse or nonmedical use only were both significantly associated with two or more substance use disorder symptoms at age 35. This association was consistent across multiple types of substance use disorders involving alcohol, cannabis, and other substances.

Another study examined the risks of future opioid abuse-related encounters in the 12 months following dental opioid prescription in adolescents and young adults using 2015 to 2016 administrative claims data. Patients who received an opioid prescription from a dentist were more likely to have a subsequent opioid abuse-related claim compared to nonexposed patients based on an ICD-9 or ICD-10 diagnosis code. Nearly 6 percent of patients who received a dental opioid prescription had an opioid abuse-related claim within a year compared to less than half a percent of those who did not receive an opioid prescription at the same time. This resulted in an adjusted risk difference of 5.3 percent after controlling for patient, race, and

ethnicity and history of past other substance use.

There are several key limitations to consider when interpreting these findings. Much of the misuse and abuse data we examined were collected by survey-based studies. As a result, there is possible inaccurate reporting or recall regarding opioid use and the reason for which opioids may have been used. Additionally, individuals with more severe substance use disorders may be underrepresented due to incarceration, homelessness, entering a treatment facility, or dropping out of high school in the case of Monitoring the Future.

In longitudinal studies, there may be confounding by indication because the surveys did not elicit the reason for which the opioid was prescribed. Emergency department data only captured cases that resulted in a visit to the emergency department. Cases resulting in death were excluded. A limitation of the poison center call data is that this analysis was restricted to single substance exposures, which may have excluded many abuse cases. Specific to administrative claim studies, the study of opioid prescriptions by dentist did not capture actual opioid use or exposure resulting from someone else's prescription. Additionally, administrative health care claims may poorly capture misuse, abuse, and substance use disorders. Deaths could have been incompletely captured as there was no linkage to mortality data. Finally, there was a potential for unmeasured confounding by undocumented family or personal history of substance abuse.

In summary, recent data indicate that approximately 3 percent of adolescents report opioid misuse or abuse in the past year. Adolescent prescription opioid misuse and abuse have been declining over the past decade. Most commonly, adolescents report obtaining misused prescription opioids from a friend or relative, usually for free. But about a third of adolescents who misused or abused opioids obtained them from their own prescription.

Among adolescents, opioid-related ED visits due to self-harm occur at similar rates as opioid-related nonmedical use. Most pediatric prescription opioid-related Poison

Control Center calls involved unintentional exposures in children ages 5 and younger. However, calls in adolescents were more likely to be due to misuse, abuse, or suicide attempts. These exposures in adolescents also resulted in more severe medical outcomes, often necessitating treatment. Additionally, calls involving adolescent suicide attempts with prescription opioids have been increasing.

Medical use of opioid analgesics may place adolescents at increased risk of future prescription opioid misuse or abuse. Additionally, prescription opioid misuse or abuse in adolescents is associated with a higher risk of substance use disorder symptoms in adulthood. But medical opioid use alone with no misuse or abuse is not a risk factor for future substance use disorder symptoms. Further research is needed to understand the relationships between medical use and future misuse, abuse, substance use disorder symptoms, and related outcomes. This concludes my presentation. Thank you.

DR. KELLY WADE: Thank you for that presentation. We'll now continue in our line of clarifying questions. Again, remember to state your name for the record before you speak. And if your question is directed at a specific presenter, please identify that presenter. We'll pick up where we left off over here with Angela.

DR. CZAJA: Thank you. Angela Czaja from Children's Hospital of Colorado. I had a couple of questions. The first was for Dr. Lloyd. I was curious about the waiver requiring pediatric studies because of low prevalence of certain conditions for some of the medications, and what's the definition of low prevalence in that situation?

DR. LLOYD: This is Josh Lloyd, FDA. I don't have a specific definition for low prevalence for you, but as part of addressing the requirements under PREA, during the development stage, companies are required to submit a pediatric study plan on how they're going to address the requirements under PREA. Then we evaluate that plan and we discuss it at the Pediatric Review Committee. And if the sponsor intends to pursue a waiver request, then

it's incumbent upon the sponsor or the company to provide data to support why the prevalence is too low to allow for studies. We evaluate those on a case-by-case basis. Some disease entities don't really occur in children. For example, osteoarthritis, things of that nature which would necessitate a waiver because it's just not possible to study those indications in kids. But basically, we evaluate the information that's contained in the pediatric study plan to see if we agree with the sponsor or not whether or not there are sufficient patients to study, but I don't have a specific threshold for you.

DR. FIELDS: I think Dr. Hausman from Office of Pediatric Therapeutics might.

DR. HAUSMAN: Yeah, hi. Ethan Hausman from DPMH. There's going to be a bit of a discussion later on this afternoon about the PREA requirements. As Dr Lloyd noted earlier, when products are coming in in the development phase before the submission of the NDA or BLA, as the case may be, in most of the situations the sponsors are required to submit a pediatric study plan that characterizes the nature of the development plan for the drug for pediatric patients. The sponsors and FDA have to come to an agreement prior to the submission of the NDA or BLA. Ellen, does that approximately cover what you had -- okay.

DR. CZAJA: Just to clarify, it's based on feasibility of conducting the studies that that prevalence is interpreted or in terms of the condition in general?

DR. FIELDS: I'm sorry. Could you speak a little bit louder?

DR. CZAJA: I just wanted to clarify, especially because so many things in pediatrics is not going to be large numbers already. So is it really based on in your discussions of whether or not to waive the requirements? So, for instance, in the opioid studies, the extended-release for 7 and under was waived because of low prevalence. So that's purely based on a practical feasibility assessment as opposed to the condition.

DR. LLOYD: This is Josh Lloyd from FDA. Yes, it's based on the low prevalence and then the feasibility for being able to actually conduct and complete the studies in

those age groups. Specifically, the waiving less than 7 approach is based on our experience with opioid products. Because originally studies were required for the entire pediatric age range and basically companies were unable to enroll patients in that age group. So, then we altered our approach to waiving less than 7 because of feasibility issues.

DR. CZAJA: Thank you. That's helpful. And then just the second question I had was actually for Ibrahim. So the data that was stratified by less than 2 -- 2 to 11, and then the adolescent 12 to 17. I was wondering if you had data in smaller age strata for the 2 to 11 age range? Mostly because I could imagine both the indication, the development as well as the rates would vary considerably from 2 to 11. So, do we have that data available? Or did you already break it down into smaller age groups from 2 to 11?

DR. IBRAHIM: So the age breakdowns that we had originally was to mirror the study, the PREA study that we're going to focus on. So, that's how we broke down the age groups. But we do not have data breaking down the age groups further down.

DR. CZAJA: I would suggest that it might be useful because it is a wide age range to go from 2 to 11. I understand the discussion in the question that's being posed to us is whether to say 2 to 11 should be approved or modified on the label, but in terms of considering the populations from 2 to 5, 6 to 11, there's probably considerable differences. So, I guess I would suggest that if we can have smaller age brackets, it would be useful information in consideration.

DR. KELLY WADE: Thank you for those questions. Howard, do you still have a question? Sorry, Richard.

DR. HOLUBKOV: I'll just be brief since this goes back to -- it's just a biostatistical observation from earlier this morning after Dr. Lloyd's presentation. There was some discussion of pain reduction and severity as an important outcome to demonstrate the efficacy. A lot of these trials uses rescue therapy. Dr. Fields noted that using the immediate

rescue design, right, and that seems beneficial for the child, right? As soon as the inferior agent or the placebo doesn't work, you introduce the rescue therapy. Now, if that design works like it's supposed to, you should see almost no difference in pain, right? You just get the transient blip in pain from the placebo arm and then, boom, you introduce the rescue therapy. And that seemed like it would be -- a beneficial design for the child may improve content rates.

So, again, I just wanted to mention, once you do that, then you can no longer directly demonstrate efficacy of the agent. You shouldn't see necessarily a difference in pain overall. So, I just wanted to point at that -- as you well know there's an intelligent selection of surrogate. In that case, you can't directly demonstrate the efficacy of the agent, but you can just particularly, exactly for the best setting, you should choose the surrogate endpoint. That would be something sparing of analgesia, a need for rescue therapy, time to rescue therapy. The best endpoint would depend on whether it's a long or short-term duration study and other factors. But I think that design is very valuable with the selection of the proper endpoint.

DR. FIELDS: So hi, it's Ellen fields. That is the design that we use in the children less than two. The endpoint isn't pain, it's the use of rescue medication. And you'd expect less rescue medication used in the group that receives the study drug. So to your point, that's what we do.

But in the older kids, as we said in the studies that only collect PK and safety data as the requirement, and also get some efficacy data, there's no control in those studies. And it's open label. So they can have rescue whenever they need it, obviously, but it's a different study design.

DR. WADE: Okay. Let's continue down this left side with Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: This is a clarification question for Dr. Greene regarding the last summary of findings. In the second point you have "but," but medical opioid

use alone with no misuse or abuse is not a risk factor for later substance use disorder. I wanted to clarify that. This is to me like you are stratifying by a factor affected by exposure.

If I understand correctly from your presentation and from the briefing materials, there seems to be data to support that prescriptions of opioids used in adolescents increase the risk of misuse and abuse, based on the reports. And that the misuse and abuse increases the later risk of substance use disorder. But your point of the medical use alone with no misuse and abuse, seems to suggest that is only one type of combination of factors.

And I wanted to clarify that the misuse and abuse is happening later, so at the time of prescribing the opioid, we do not know who is going to go one path or another. So prescribing opioids based on the data provided increases the risk of later substance use disorder in adulthood. Correct?

DR. GREENE: Yeah, that is actually correct. Based on the studies, what we're seeing is that in the studies that looked at prescription opioid medical use in adolescence, and they looked at misuse, let's say, in young adulthood, so around age 19 to 23 as well as in early midlife around age 35, there did seem to be an association with future misuse or abuse. However, we did not see that when we looked at substance use disorder as the outcome. So there was really no increased risk of substance use disorder at age 35 if somebody had reported that they had used opioids as medically directed at the age of 18. So I think, yes, I believe that you are probably correct, that it does have to do with the timing. Like what kind of exposure -- or how they're using the opioids at that time of adolescence.

DR. WADE: Thank you. Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: Thank you. The question's for Dr. Greene. A two-and-a-half-part question. So linking slides number 11 and 15; how does the annual rate of self-harm or prescription for opioids, when used for self-harm, compares to rates of use of self-harm

for other prescription drugs with similar safety profiles? And related to the outcomes, is death or long-term morbidity any different than for other drugs of similar safety profile?

DR. GREENE: I'm sorry, can you repeat the question please?

DR. ORTIZ-AGUAYO: So first part of question one; how does the annual rate of self-harm compares to rates of use of self-harm for other prescription drugs with similar safety profile as opioids? So, how often are kids using other drugs to harm themselves?

DR. GREENE: So, in this particular analysis we did not focus on that. But I am sure that we can look into that further.

DR. ORTIZ-AGUAYO: And then when we're looking at the mortality and morbidity, it's similar question. Do we know that the risk for death or significant long-term morbidity is higher with opioids than with other prescription drugs?

DR. GREENE: Again, I would not have that information at this time.

DR. ORTIZ-AGUAYO: Okay.

DR. GREENE: Thank you.

DR. ORTIZ-AGUAYO: Thank you. And then thinking on Question number 20 -- I'm sorry, slide number 20, and trying to mull over a little bit around the issue with the dental prescriptions. I'm unsure if there's any factor analysis, but does the data suggests that there are any potential modifiable factors that are associated to the development of misuse, such as initial dose, length of exposure? And the reason why I think about that is that could inform the content of the label with regards to risk benefit analysis and patient education.

DR. GREENE: So, based on that study, I don't believe that there was any information that concluded that there was an association with the dose. It seemed to be that the associations with the risk of abuse-related claims tended to be based on patient age; so younger patients were more likely to have an abuse-related claim, and if they had a past history of other substance use. Thanks.

DR. TERRI VOEPEL-LEWIS: I'm Terri Voepel-Lewis. My question and comments are directed at Dr. Greene. My colleagues at University of Michigan have gathered a lot of this data on misuse and abuse. And I want to reemphasize that the definition of misuse doesn't necessarily include kids using their own medication long-term beyond the time when the physician prescribed it, so they go back to the cabinet again and again and again for the same kind of pain. That may underreport that type of misuse. So those data may underreport that type of misuse, which then can lead to later dependence and future misuse.

The other thing that I just want to clarify about those data, is there are data out there on the motivations for misuse. And I know that your presentation didn't really address that, but the motivations related to pain management or self-pain management are pretty high in the adolescent population. And I'm really interested in how kids who try to self-manage pain again and again and again, with opioids, then go on to misuse and abuse later. I just want to know if you can comment on that, and whether or not the labeling needs to better address the potential for misuse in these younger kids who go on to try to self-manage their own pain. And there's other data out there, by the way, that also talk about kids with chronic pain, that then have the potential to misuse and abuse medications later in life.

My last comment would be with the McCabe data on the substance use disorder later in life. Those data were prone to lots and lots of dropouts so they may underreport substance use disorder in adults. Because number one, those patients who did misuse or abuse after medical use, may have died or may have dropped out of that study. Because I think the follow up rate was pretty low.

DR. GREENE: So, in this analysis and particularly, we did not look at the motives behind the misuse or abuse. So a lot of the statistics that we are reporting on the figures for misuse and abuse in adolescence kind of don't take the motive into account; you know, whether they were trying to treat for chronic pain or whether it came from their own prescription.

DR. WADE: Thank you for raising those points. If I can just remind people to state their name before your question, and to speak into the microphone so that everyone in the room can hear. We'll continue around the table with Dr. Hoehn.

DR. HOEHN: Sarah Hoehn. This is a follow up to a question for Dr. Greene. When we think about what we think the labeling should be this afternoon, we want to think about whether or not there should be any recommendations about Narcan in the household when there's long-acting opioids.

To me there's public health implications in distinguishing between who's a household relative versus who is a friend. And in all of the slides, I think it was everything where we talked about the abuse and misuse, they combined friends and relatives. And to me from a public health perspective, there's a big difference if they're getting it from their mother or father or brother or sister, in the same household, versus getting it in the high school bathroom.

I don't know if there's a way to tease out in that dataset who's like a household relative versus who's a friend from down the street. Because I do think there's a distinguishing -- there's potential implications for that. So my specific question about that for Dr. Greene is, is there a way to tease out and separate out who was in fact a relative in the same household versus who is a friend?

DR. GREENE: So actually in the "Monitoring the Future" survey -- and this wasn't displayed in the slide just for kind of brevity, because there wasn't enough room really. But in table seven of the background package, specifically in our review, they do make a distinction between given for free by a friend or given for free by a relative. And it does seem like there is much more of a burden of them getting the prescription opioids for free from a friend.

DR. MCANINCH: Page 114 of the background package.

DR. WADE: Thank you for that. Dr. Flick.

DR. FLICK: Just a little bit of a follow up to that question and a previous request for information. So Dr. Greene, on slide 23, you said most commonly adolescents obtain prescription opioids from a friend or relative as we talked about. The availability of those opioids are directly related to unused tablets or medication from a previous prescription.

One of the efforts that's underway from AAP and from a lot of others, is to reduce the size of the prescription. Earlier there was a request from one of the panel members to better understand. And I think the data that would be very helpful would be to understand trends in the number of tablets per prescription written.

So we have data on prescriptions, and there may be data available on the number of tablets. If we could do the math and find out what the trends are in the size of those prescription or the number of tablets prescribed, I think it would be very helpful for us to know whether those efforts around reducing the size of prescriptions -- in other words, frequently children and adults were given far more than they really needed. And so, if those data are available it would be particularly helpful I think.

DR. STAFFA: This is Judy Staffa. There is a lot of literature on that, actually following up with patients -- I'm not sure if it's in the pediatric realm, specifically, but in general there's a lot of studies and literature talking about looking at what patients receive versus what they use. And every study across the board, whatever indication has been looked at, what they receive greatly exceeds what they use.

And so actually we've been looking at that literature. Because as you know in other spaces we actually have put out a Federal Register Notice, thinking about whether we could require packaging of smaller amounts, to help facilitate that ability to easily prescribe smaller amounts. So that's an effort that's in progress. But it's not solely in the pediatric space, it's just in general.

DR. FLICK: Clearly not. There is literature in the pediatric space around that. And one wonders whether that could be part of the labeling, that minimum numbers of tablets should be prescribed or something to that effect. But again, we see this significant decline in the number of prescriptions over time, it would be useful for us to know whether the size of those prescriptions, or the number of tablets dispensed, also decreased.

DR. STAFFA: This is Judy Staffa again. We have looked at that in -- again, for other discussions. We'll see if we can pull any of that and share it if possible.

DR. WADE: Dr. Jones.

DR. JONES: I have another clarifying question for Dr. Greene. In the three studies that you discuss for the literature review, I just wanted to confirm that none of those studies took into account a total exposure to the drug. So none of those studies took into account the dose that the patients received or the duration that they were on the medication?

DR. GREENE: Yes, that is correct. Those studies did not take that into account, if you're referring to the McCabe studies and the Miech study.

DR. JONES: Yeah.

DR. GREENE: Yes. They just looked at basically whether -- they surveyed the students and looked at whether they had used prescription opioids in the past, medically or nonmedically.

DR. JONES: Thank you.

DR. OSTER: Randi Oster, consumer representative. This is a question for Dr. Greene. In summary it says very clearly that the students are at increased risk for abuse and misuse. And my question is, at what point are they addicted? And when do we know that maybe they're abusing and misusing because of an addiction? And how many pills, and how frequently do they have to have a prescription, before it translates from misuse and abuse, but to need, and that need is addiction?

DR. GREENE: Those studies and our literature review didn't really investigate that particularly. So that would be another body of literature that we did not look into at this time. However, that is a very interesting question and I do agree it's something that should be looked into.

DR. MCANINCH: Jana McAninch. I just wanted to add to that; and to say that I think what you're asking is kind of the million-dollar question, you know, when that transition is happening. But in terms of the studies and the way they measure the outcomes, really, here, self-reported, misuse and abuse is referring to a set of behaviors, and that's very broadly defined. Whereas substance use disorder is a clinical diagnosis relating to repeated uncontrolled use and adverse consequences occurring because of that use. So there's sort of different concepts, but obviously there's a lot of overlap.

DR. OSTER: Right. But for this afternoon for labeling, we have to look at the information we have available today and make sure that we consider the results that you're telling us here. Thank you.

DR. WADE: Are there any other questions? Dr. Turer.

DR. TURER: Christy Turer. The thing that I'm wondering, and in part driven by my experience in internal medicine, if I want to prescribe an opioid to an adult patient, when I prescribe that I cannot approve that prescription unless I go through the Texas Prescription Monitoring Program and I've reviewed the history. Now we have a beautiful -- I mean, this is a great example of an excellent clinical decision support system, in that when I put in that prescription and try to hit sign, I can't sign until I've reviewed that. But it brings it up automatically, it's got my login already linked to it so that I can do it. So I think in pediatrics where that is not in place, I think that that may be one way to really help prescribers.

But in terms of the labeling, one thing that went through my head is when we do an X ray on an adolescent, a female adolescent, we get a pregnancy screen. In adolescence to

whom we may be prescribing opioids, might it be feasible to actually do a urine drug screen? And also in adults, before we put somebody on an opioid -- be it for osteoarthritis or et cetera -- in the low income, high-risk group with whom we work, we always do a pain contract, irrespective of whether we think that persons is at risk. We get urine drug screens on them regularly and we develop a pain contract.

So those may be things that could be -- you know, in terms of we have REMS for other drugs. Given those data that were just presented about the high risk of misuse and abuse, particularly when there's been a past history of use, these may be feasible ways of getting to the heart of this problem.

The other thing I wonder in part, from the familial misuse, is just as we do with adults we have a history of their prescriptions. Like if they've ever gotten a prescription, I can see if they've gotten it 10 years ago. Being able to do that on a family level. So knowing if an adult has a prescription drug, or sibling who has sickle cell or cancer has gotten an opioid. So that just like we do anticipatory guidance about do you have a gun in your home; we could have anticipatory guidance about do you have opioids in your home.

DR. WADE: Stephen.

DR. PATRICK: Stephen Patrick from Vanderbilt. Just a quick comment. So 49 states now have PDMP. And I'm not -- while it varies state to state, I think pediatricians have the same sort of requirement in terms of testing.

And the other comment is just about the complexity. We're talking, rightly so, about opioid supply and adolescence, but the development of addiction in adolescence is complex. And just untreated mental health disorders by themselves is a risk factor for opioid use disorder. And we've seen this explosion in recent year of untreated mental health disorders in children, It's massive increases in admissions to pediatric hospitals around the country.

And so there's just complexity around this that's sort of beyond even just opioid prescribing that we see. And while it doesn't relate necessarily, we still have to consider how with the relationship of opioid supply, there is this sort of greater context and complexity to the opioid crisis in terms of mental health disorders among adolescents increasing, and the complexity opioid crisis that now is shifting to heroin and fentanyl.

DR. WADE: Thank you for that Dr. Patrick. Dr. Griffin.

DR. GRIFFIN: Marie Griffin, Vanderbilt. I don't want to beat a dead horse, but we heard a lot of comments, Dr. Greene, about your statement about medical use does not result in substance use disorder. And I think it's just a little bit jarring because it sounds so definitive. The confidence intervals on that analysis were pretty wide and the point estimate was actually above 1.

I think it would just be -- it would sit better with me anyway if it was, we don't have the evidence for this, we don't know. But to say that it does not result in substance use disorder just doesn't really -- I don't think we have the evidence to say that. Does that make sense?

DR. MCANINCH: Jana McAninch. I just wanted to clarify that what she was saying was that -- and I think Dr. Hernandez-Diaz also made this point. Was that in that study they looked at a population who reported medical use only with no misuse or abuse. And that was not associated with substance use disorder at a later time. But obviously, that's selecting for a lower risk group who is not prone to misuse and abuse during adolescence when they were exposed to opioids. I think there was a good point that when someone is prescribing the medication, you don't know which group your patient falls into. Are they only going to use the medication as directed or are they going to potentially misuse it?

I think she was just trying to describe the results of that study. But I think your point is well taken, that there are many caveats.

DR. GRIFFIN: Yeah. I agree that that's what that study showed. But I think -- it's just, again, when you have a summary and you say this does not do this, it's a little misleading if I'm just reading the summary results. It's we don't have that evidence yet or there's been only one study of this, and it didn't show it -- anyway.

DR. WADE: Well, I'd like to thank the members of the FDA for putting this morning session together to give us the context of opioid use and outcomes and the difficulties of pediatric studies. Thank the members of the committee for this robust discussion. We'll now take a 60-minute break for lunch and readjourn in this room at 1:00. Again, there is a reminder to the panel members that there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. And again we'll resume at 1:00.

[LUNCH BREAK]

OPEN PUBLIC HEARING

DR. WADE: Welcome back, everyone and thank you for everyone's attention to time as we cover this material today. At the beginning of this afternoon session, I'd like to state that both the Food and Drug Administration and the public believe in a transparent process for information gathering and to ensure such transparency at the open public hearing session of the Advisory Committee Meeting. The FDA believes that this is important to understand the context of an individual's presentation; and for this reason the FDA encourages you, the open public hearing speaker, at the beginning of your written and oral statement to advise the Committee of any financial relationship that you may have with the sponsor, its product and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance

at this meeting.

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

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

At this point, will speaker number one step up to the podium and introduce yourself. State your name and any organization that you are representing for the record.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research which is a nonprofit think tank that focuses on conducting and scrutinizing research that has implications for public health. We do not accept funding from pharmaceutical or device companies, so I have no conflicts of interest today. Also, I just want to say my perspective is as someone trained in epidemiology at Yale, who is a faculty member at Vassar and Yale, a researcher at Harvard, a fellow in bioethics at the University of Pennsylvania, and worked in Congress for a dozen years as well. So that's my perspective.

Also last week, I was here in the same room at a meeting for FDA officials who were asking for perspectives on opioid standards. What kind of standards should be used in future research? And it really concerns me that there's quite a disconnect between the discussion we had last week, with the FDA officials talking about the need for better research

and how that can help reduce addiction and other problems with the opioid epidemic, and some of the standards that seem to be considered today. So I want to talk about that a little bit.

First of all, there's been some discussion about, well we already know about efficacy in adults, so we don't really need data on efficacy in children. And that, to me, just seems incorrect for a variety of reasons: One is that we increasingly know that some of the opioids that were approved by the FDA weren't as effective as we had thought that they were; and when compared for example, for chronic pain, to over-the-counter medications, some of the opioids are no better. For that reason we should be particularly concerned, especially in the context of what the risks are for children. We should be demanding better research to compare opioids with other analgesics for children of all ages.

I especially want to mention that the standards that were used for adults for opioids was something called enriched enrollment. This is a type of statistical analysis where only patients who had already shown that they were responding to opioids were included. And any patients who did not do well with opioids were excluded from the study. So you had a very biased sample where virtually all of the patients involved had at least some ability to respond to the opioids; and the ones who didn't were excluded from these studies of adults. And that might help explain why two-thirds of the kids, in one of the studies that you've looked at today, did not respond, did not show any benefit, and that's why they dropped out of the study that they were in on Opana.

It's also important to remember that we don't know what the impact is on brain development, but we know that children's brains are more flexible and vulnerable than adults. We know that MRIs have shown that opioids can change brains of adults, and so it would certainly be important to have some data on children pertaining to brain development both in terms of what testing can tell us but also what happens to the children over time.

And, in addition to not having short term, well designed clinical trials, we don't

have any long-term data at all. In short, the pharmacokinetic data is just not enough, should not be enough. As somebody's already mentioned, the need for more genetic information, but also the studies are just too small. Some of the samples were eight children getting a particular dosage. And those are eight children in different sexes and different races. And so we really don't know who's benefitting more, who's more at risk, and the studies are too small to tell us that even if they were better-designed studies. The fact that they were two patients who had excessive exposure means that eight percent were -- I don't think we can just dismiss those as outliers. I also want to mention that all 61 of the children in that study, ages 2 through 12, had protocol deviations a hundred percent that didn't do all the assessments that were supposed to be done. And, if that happens in a clinical trial, what happens in real life?

Just to mention about the labels, they're way too long. They are so long. Who's going to read them? I mean they are dozens and dozens of pages long. They're obviously not for patients to use, but also a lot of physicians aren't going to read them all and they're not going to get the information they need. REMS could be very helpful in including better data to require a patient booklet or a checklist that parents would need to sign before their children get these drugs.

And I just want to say I think that companies that want an indication for children for their opioids should be required to do the studies that prove that their product has benefits that outweigh the risks from those patients. Just remember, in a clinical trial if the child doesn't respond to the opioid they can just stop taking it. But in the real world if they need an opioid -- or if they need a painkiller, I should say -- and it's not effective, it precludes them from getting a different painkiller for some period of time or at least potentially will.

So, in short and in conclusion, I think that we've learned from what's happened with the opioid epidemic that looking through rose-colored glasses is not the best way to make sure that there's safety and effectiveness of the products that the FDA is approving. You've

asked great questions. And I urge you to really focus on what we need to know and how can we find that out, and what can we do in labels to prevent kids, and doctors and family members from assuming that a product is safe and effective for their children. And I'll be glad to answer any questions. Thank you.

DR. WADE: And now I'd like to ask if speaker number two will step up to the podium, introduce yourself and please state your name and any organization you are representing for the record.

DR. CHATTERJEE: Hi. My name is Dr. Neil Chatterjee. I do not have any financial relationships or any conflicts of interest. I definitely understand the situation that we're in; and unfortunately, until we discover a drug that is better than opiate, we're kind of stuck in this chronic pain section of medicine. It's a very subjective decision, especially in the pediatric population.

One of the things that I've realized in research and looking at these different doctors, is that there's too much emphasis on that one to ten scale. What does that mean? They ask the parent. They ask the mother, the father, and we are trained in the '90s and 2000s to treat pain as a vital sign. And what happened with that, is that we're in a rush in hospitals to discharge patients with a lower score. And that culture kind of contributed to the crisis that we're in.

And so we need to use age-appropriate functional scores for the pediatric population. We need to ask the parents of a nine-month with sickle cell anemia if we believe that they're in pain, what is the function? So are they feeding better? Are they acting better? Are they sleeping better? So we need to focus more on this.

And oftentimes what's happening is that the pendulum's swinging left and right, right. So, before, pediatric pain specialists were definitely treating most of their children with opioids; and then with all the new regulations at the CDC and everything, a lot of pediatric

pediatricians have stopped, have seized from dispensing any controlled substances. So I went over that.

And one of the things that we need to do, checklists worked -- Atul Gawande, the author of the book about checklists in surgery. We need to do the same thing when we are treating a patient with a subjective conditions, whether it's a controlled substance for anxiety, whether it's a controlled substance for ADHD or for chronic pain, we need to make sure we're doing our due diligence to make sure that those patients do indeed need those medications.

Another problem is we have multiple providers, and in this case we're talking about chronic pain. So the eight-year-old with osteosarcoma, who's on long-acting narcotics now goes to a psychiatrist, is treated for anxiety, given some Xanax. So we need to definitely communicate better in this population particularly. One of the things that I'm just unsure why this is happening, is that we don't have an alert system; meaning that if a patient does fill another controlled substance, I should know that information as their doctor or any physician who's treating that patient.

Also we all know about the PDMP, the Prescription Drug Monitoring Program. They're not very effective, they're inefficient, and we're scrambling all the time eyeballing trying to find out what medication the patient is receiving from the pharmacy. And it takes a lot of time. And what happens is that opioids leak, or other controlled substances in general leak into the open market. So you have a family member who's five, who's medications are in the medicine cabinet not locked up. And their brother's or sister's teenager friends comes and gets ahold of them. That is what we're seeing.

One latest study shows that 100 percent of patients in the pediatric population under 18 were addicted from a prescribed controlled substance. That's where it starts. So we need to be more efficient and integrated into our workflows. Because right now physicians just do not want to prescribe any controlled substances. That's not really the right thing to do. And

just to discuss this, diversion, we need better safety measures for sure. We need to be able to interview the family members. We need to educate them better. And honestly, there's just no time in the workflow for the physician with all the background checks that they have to do.

So, in general, just basically, we need to reduce the misuse. This is where it starts in the pediatric population. It's a crisis and we need to help curb this addiction risk. The tracking system is, like I said, very inefficient, and we need to come up with better methods for the provider to find out what medications the pediatric population is in to prevent the leakage onto the open market. What we really, really need to do is we can improve the tracking and monitoring of controlled substances, and make sure that the pediatric population is getting the right information. The safety information, the risks and benefits are all outweighed in the physician's office. And just changing the culture of how we dispense and prescribe controlled substances, especially opioids. Thank you. My time is up so, any questions? All right. Thank you.

DR. WADE: Thank you to both speakers for coming to the open hearing today. Is there anyone else in the audience who was planning on speaking today? Great. So, at this point, we will continue with our regularly scheduled session. The open public hearing will officially close at 2:00 pm, and we'll have an announcement at that time. But I'd like to continue the discussion that we had this morning. I know we have a question from Dr. Callahan. But before we move to that, I would like to turn over the conversation to Dr. McCune who has some information for us, and her colleagues who were able to pull some information that was requested earlier this morning.

CLARIFYING QUESTIONS/DISCUSSION

DR. MCCUNE: So thank you very much and thank you for the discussion this

morning. I wanted to just follow up on a couple of items, and then I'll turn it over to Dr. Staffa.

One of the questions that came up was the definition of extrapolation. For the FDA, the definition is that during the course of the disease, that the course of the disease and the drug's effects are sufficiently similar in two populations to be able to extrapolate the information. Generally, this is using adult data where effectiveness can be extrapolated from adequate and well-controlled studies usually in adults. And this is then supplemented with information obtained in pediatric patients such as PK information and safety. Although there can also be extrapolation from older pediatric patient populations to younger pediatric populations. I think that the review division will talk a little bit more about extrapolation in general in this population.

And then I just wanted to remind folks that we've been talking about information in FDA labels, but you've also been talking about things that would be considered the practice of medicine. And the FDA does not regulate the practice of medicine. So as you're thinking about these issues, in terms of what's actually information in the label versus what would be practice of medicine, just a reminder there. And I think Dr. Staffa was going to talk about some of the questions.

DR. STAFFA: Hi. Judy Staffa here. I just wanted to give some very general responses to some of the questions that came up. I know they weren't exactly what we're going to be talking about, but just trying to make sure everybody's comfortable that they have a clue about they wanted to know about.

One of the questions that came up was about naloxone and naloxone use in kids. So, again, I can point you to -- we had a public meeting here -- actually in this room -- in December to talk about how FDA can get more naloxone out there. And during that meeting, we presented some data on prescriptions of naloxone. And there's a table up here that actually breaks down those prescriptions by age.

So the rows you can see that starts with the youngest children on the top and then it goes all the way down to the oldest children -- 65 plus -- on the bottom row, and then it breaks it down by product. So you can see that a very small percentage of naloxone is being dispensed in outpatient pharmacies to kids. It's kind of commensurate with the amount of opioid if you look at it as a percentage of all the opioid out there.

So I'm not sure. And, again, it breaks it down by dosage. I know there's a specific interest in the nasal spray, and you can see that row as well. So it's a very small amount right now. And we had the meeting in December. We got input from the committees, and we're in the process of having internal discussions about what mechanisms we can do to get more naloxone out there. So that's ongoing.

The second thing I wanted to touch base on was, I think, Dr. Flick had brought up the question about prescriptions are dropping, what about the number of tablets? Or maybe it was Dr. Meisel. I don't have the details about tablets per prescription, but of course with the variation there, any summary measure isn't going to be so great anyway. But I can tell you that in the last five years the total number of tablets being dispensed in outpatient pharmacies has been coming down as well, about a third drop. And again those are ballpark numbers. But it should be somewhat reassuring that all prescription volume -- as the number of prescriptions have come down, the total volume of pills has also come down somewhat. I hope that at least -- I know nobody's ever happy with high-level numbers. And I see Dr. Meisel's microphone lighting up.

DR. MEISEL: Just to clarify with that, I know you can't really answer this definitively, but I'll ask you to speculate. We saw a 75 percent reduction, give or take, in the number of patients with a prescription in this population. And now you're talking about a thirtyish -- 35 percent, decrease in the number of tablets. Would it be fair to assume that the opioid load, if you will, in the sub-18 age population is actually decreased by greater than 75

percent?

DR. STAFFA: I can't really speculate on that because the 30 percent I'm talking about is really more -- it's all ages. It's all prescriptions. It's not specific to pediatric. And again, much of pediatric use, as in much of use in all ages, is acute prescriptions, right, not necessarily -- chronic use makes up a smaller percentage of the whole.

DR. WADE: Well, thank you for the follow-up to our posed questions this morning. That was really, really helpful and wonderful for you to be able to provide that table to us. Before we move into the scheduled talks, I want to make sure we handle some remaining questions. Dr. Callahan.

DR. CALLAHAN: David Callahan. I have a comment and a question. My comment is, in my community a lot of our patients ask where they can dispose of their drugs, and there is no place where they can dispose of them. The pharmacies will not take them back and the hospitals will not take them either. My question is, I've seen data on this before on stimulants prescribed for children being diverted by parents. Is that common with narcotics? Do we know how many of the prescriptions or how much of the prescription for these narcotics for kids is being taken by parents or other adults; how much does the child actually use, and how much is used by other people illicitly?

DR. STAFFA: This is Judy Staffa. I don't think we have any data on that, but clearly it's an issue and it's a concern. All diversion would be a concern. And FDA has some new authorities in the area of packaging and storage and disposal. And we're exploring whether there are ways we can use those authorities to help improve the situation. We're working in that area.

DR. WADE: Dr. Turer.

DR. TURER: Christy Turer. What I'd really value is clarification on the role of FDA in the REMS development, so in the risk evaluation management, if it's left up to the

companies or to clarify Dr. McCune's statement about medical practice versus outside of that. If I could get a little more direction on that, I'd greatly value it.

DR. STAFFA: Judy Staffa again. Yeah, FDA oversees REMS. These are risk evaluation mitigation strategies. If a drug at approval is determined that the benefit will outweigh the risk, only if there is a strategy in place to ensure that, then FDA -- either the sponsor will propose a REMS or FDA will require a REMS. And that is worked out prior to the drug is approved.

Once the drug is approved under a REMS, the REMS is spelled out as to how the drug will be used. The sponsor is required to evaluate the REMS and to submit that on a prescribed schedule to FDA. That can also happen after a drug is on the market. If a safety issue is identified and it's determined that the benefit only outweighs the risk under certain conditions, then the REMS can be imposed post-approval as well. But, yeah, that is under FDA's statutory authorities.

DR. WADE: Go ahead.

DR. VOEPEL-LEWIS: Terri Voepel-Lewis. I want to go back to -- the Speaker one just raised an issue for me that sort of takes me back to, I think it was, Dr. Patrick's question about what is the bar for labeling or for approving pediatric studies. And I wasn't aware of a meeting last week that she referred to that seemed to be discussing labeling for opioids or approving opioids in general. So my question would be, what is the bar, the minimum bar, for efficacy and safety for opioid studies, and what's the bar for labeling? Like what is it -- obviously, there's probably some guidance for what has to go on a label, but what's the bar? What absolutely has to be there? And how does that reflect the uncertainty that seems to be so prevalent in the pediatric drug data?

DR. FIELDS: Hi. It's Ellen Fields. Are you referring to pediatrics or adults?

DR. VOEPEL-LEWIS: Well, to me the bar for pediatrics needs to be at least as

rigorous as adults if not more so. So are there a minimum number of patients? Do we have to meet particular sample size? What is required by the industry in order to get a drug labeled for its use? And let's talk about scheduled medications. It could be any scheduled medication, opioid medications, whatever.

DR. FIELDS: I think I understand your question. It depends on what the drug is. If it's a novel opioid that is a drug that's never been approved, the drug substance isn't approved, generally, we would require two adequate and well-controlled clinical trials to demonstrate efficacy. The number of patients in the clinical trials to demonstrate efficacy depends on -- the study has to be powered for the expected treatment effect. There's no specific number of people in an efficacy trial, and I'm sure the statisticians can speak to this as well. It depends on what you expect the treatment effect to be and a number of other things.

We do require a safety database. In addition, usually there's additional exposures in the clinical development program in adults. And for a new molecular entity we would generally require at least 1500 patients being exposed to the drug, in the absence of any serious or unexpected adverse event, then we may require even more people.

Most opioids that have been approved in recent years are not new molecular entities; they're reformulations of already approved drugs. For example, it's an extended-release formulation being approved, but there's already an immediate-release formulation. Generally, what we've done in that setting is require one efficacy study, and that's mostly to -- because we know it's an analgesic, so the efficacy study is mostly to define the dosing interval and to look as well for safety signals that maybe there. And we would require some safety database. I mean, if it's a drug that's been an immediate-release formulation for a long time, there's a range of numbers we would use for the safety database depending on the molecule. The abuse-deterrent opioids that have been approved with abuse-deterrent labeling, most of them are reformulations of already approved extended-release form- -- most of them are extended-release

and most of them are reformulations. If they reference, there's a way for a drug to be approved where they can reference an already approved drug.

So it's a little complicated, but if they're bioequivalent to an already approved -- so if there's a new morphine product that's bioequivalent to an already approved morphine product, you'd expect the efficacy and the safety to be the same unless there's something else in the formulation that could be a cause for a safety concern. But, in the absence of that, they wouldn't have to do any efficacy studies; they would have to do a pharmacokinetic study to show that they're bioequivalent. And, for abuse determinant labeling, there are a number of human abuse potential studies that need to be done. So there's a range of what's required for approval of an opioid depending on whether it's a new molecule, an old molecule, and what's already been approved.

DR. VOEPEL-LEWIS: So then when you're extrapolating adult data to pediatrics and if there's not -- I think you mentioned 1500 required for safety of a new opioid, a new formulation of an opioid, what criteria then do you use to say that they can label it as safe.

DR. FIELDS: For children?

DR. VOEPEL-LEWIS: For children.

DR. FIELDS: Well, we have a lot of discussions internally about how many to require and what patient enrollment to require for pediatric studies. It's extraordinarily hard to enroll pediatric patients in studies for analgesics, and so in order to -- so we've had a range. The OxyContin data which is public -- they eked out I think about 120 patients enrolled in the study, and it took them four years to get that many patients. And that was through the whole age range of 7 to 17. And from 7 to 11, I think there were 2 or 3. So it's a huge challenge.

There are a number of reasons for those challenges. For opioids that have -- there's a lot of experience -- say morphine used in children, fentanyl used in children off label, and others -- in addition to exposing X number of subjects or patients, we would allow some

literature support for the safety in pediatric patients because there's literature out there that talks about the use of opioids in children.

So to give you a fixed number, we don't have a fixed number but it's getting harder and harder to enroll patients, and the study sites will tell you that, you know, we've already done an OxyContin study. We can't do a -- there are not available patients for the next opioid. And there's a number of other reasons that it's very difficult to enroll. So we're trying to get the data in the label, the PK data, and the safety data we're able to get and put in the label so that prescribers have some information on dosing and PK and safety. In the ideal world, sure it would be wonderful to get 500 children to be in a study for the safety of OxyContin or another drug, but it's just not practical. I hope I was able to answer your question.

DR. VOEPEL-LEWIS: Mm-hmm. And is there any difference in a prescriber's use in the hospital versus sending it home with a parent? Sending a prescription home with a parent or a family to use at home.

DR. FIELDS: In terms of studies?

DR. VOEPEL-LEWIS: Yeah, so for studies -- for approving -- to prescribe it for home use versus prescri- -- like fentanyl and morphine are mostly used, primarily used in the hospital setting under monitored situations, whereas, giving a prescription for oxycodone for home use is a little bit different. So I'm just wondering if there's -- I'm just again asking about the bar.

DR. FIELDS: Correct. Sure. Well, it would be a different patient population. It would be, say sprains and strains or fractures or trauma that patients take the medication at home. There are unfortunately many entities -- molecules that were approved prior to PREA, and so they are not subject to the requirements. And so we can't make them do studies. But yes, the studies would be slightly different.

DR. WADE: That was helpful. Thank you. Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: I'm asking this question now because it relates to the comparison with data from the adult population not in the methods necessarily but on the results. And I was having trouble using the PK data in that it gives us important information on exposure and the dose and use that for efficacy. And it has been mentioned a few times how we can use it to make the connection with the efficacy in the adult population. And I was wondering if you know how did similar studies for PK look in the adults? Because of a lack of efficacy of around 50 percent even after selecting a group that was responding to opioids would be considered acceptable efficacy. And we can say that, therefore, there is efficacy in the pediatric population. I'm not sure I'm being clear but in -- who are using the PK studies that are not meant to give information on efficacy necessarily but with some measure of it but the very large proportion that discontinued because of a lack of efficacy. So the only information we had from those studies about efficacy reflect a rather good efficacy. Is that comparable to what we would see in adults?

DR. FIELDS: So I just want to restate it to make sure I understood. So you're saying that in the adult studies, we have an enriched population and we're taking that PK and then applying it to children?

DR. HERNANDEZ-DIAZ: No, in the pediatric data that we saw from the PK studies, there were children that were responding to opioids, that had responded to opioids, right? And then we saw that a few of them in each of the doses, and there was a large proportion of them that discontinued the protocols because of lack of efficacy, right, say 50 percent. And I was wondering to say that it is the dose efficacy as much as in the non-pediatric population if we would expect also that only 50 percent of adults will respond to treatment.

DR. LLOYD: Hi. This is Josh Lloyd, FDA. So I think it actually would be most helpful if we, after the presentation, if we go over that information and then take a look at what we have to present about that issue and then discuss the clarifying question afterwards because

I'm going to be presenting some of the information about the efficacy results that we're seeing the Opana study that you're referencing as well as some other clinical considerations in adults versus kids and why the sponsor may have demonstrated comparable exposures but we're not necessarily seeing the efficacy of those same exposures in kids.

DR. WADE: Thank you for that. As we get ready to move into the OxyContin safety reviews, I'm going to ask Dr. Patrick to give us our last clarifying question in the general domain.

DR. PATRICK: No pressure. Stephen Patrick from Vanderbilt. So my question is just general about pediatric studies and one of the questions you mentioned, the difficulty in enrolling particularly rare populations, and what sort of infrastructure is there? You know this is something we struggle with kids with chronic conditions that we see in our children's hospitals. Is this done each time a new drug is gone through? Is there an infrastructure to engage, in particular children's hospitals, that have complex care teams and palliative care teams. Is there an infrastructure there that I just don't know about, or has there been some consideration for clinical trials network of some sort in that context?

DR. MCCUNE: Dr. Susan McCune, FDA. I can maybe take a little stab at that. Clearly, if you listen to Dr. Woodcock and a lot of other folks at the FDA, as we do clinical trials or as clinical trials are done and the house is built to do those clinical trials, as soon as a clinical trial is done, the house is razed to the ground and then two weeks later, someone comes along and builds the same house. We're trying very hard not to rebuild the house. And so, about three years ago, we put out an RFA for a global pediatric clinical trial infrastructure grant to help support some of these efforts and have funded for the last three years now a grant to the Duke Clinical Research Institute and the IACT -- or Institute for Advanced Clinical Trials for Children -- who are both working in this space kind of in the academic and industry space to create a number of sites and infrastructure with informed consent documents and contracting

and those kinds of things that are done on a uniform level so that everyone can take advantage of those and then be able to do the trials from that infrastructure. And I think Ron might be able to talk to that as well.

DR. PORTMAN: Right, so industry also is supporting financially IACT. And we're hoping for a global pediatric clinical trials network. IMI2 process in Europe, the European Commission, is funding a European pediatric network. There's one in Japan. There's a Nason (phonetic) one in China, Australia, New Zealand, and some are starting in South America. So hopefully in a decade, we're actually going to have a Global Pediatric Trial Network that will be able to do drug trials for industry and for non-industry.

DR. WADE: Great. With that background of our robust discussion of all this opioid background information and pediatric labeling, we're going to now move the afternoon into our two presentations specific to the OxyContin safety review. I think we'll have these two presentations, and, after these two, we'll then have some time for clarifying questions if there's time on OxyContin.

PEDIATRIC UTILIZATION PATTERNS OF SINGLE-INGREDIENT OXYCODONE (EXTENDED RELEASE AND IMMEDIATE RELEASE), 2013 – 2018

DR. BAK: Good afternoon. My name is Daniel Bak. I'm a drug utilization analyst at the Division of Epidemiology in the Office of Surveillance and Epidemiology. I will be presenting on recent drug use patterns of single-ingredient oxycodone focusing on use by pediatric patients.

In August 2015, OxyContin was approved to include pediatric labeling in opioid-tolerant patients 11 years of age and older who are already receiving and tolerating a minimum daily opioid dose of at least 20 milligrams of oxycodone. Our view of pediatric drug utilization

patterns for single-ingredient oxycodone was in pursuant to the Best Pharmaceuticals for Children Act, which establishes that studies are performed on approved drugs in the pediatric population.

The outline of the presentation will be as follows: First, I'll provide a general overview of the outpatient use of single-ingredient oxycodone ER and IR, followed by pediatric utilization of both products in the outpatient retail setting. I will then present our findings on top prescriber specialties as well as diagnoses associated with the use of single-ingredient oxycodone and end with the limitations in a report on one of the sponsor's post-marketing requirement studies.

The settings of care where single-ingredient oxycodone was primarily utilized in 2018 was determined based on sales volume from manufacturers using IQVIA National Sales Perspective database. Single-ingredient oxycodone was distributed primarily to the retail pharmacy setting in 2018, therefore, we focused our analysis on the outpatient retail pharmacy setting.

To conduct these analyses, we used a variety of proprietary databases to measure the dispensing of prescriptions from outpatient retail pharmacies to patients. This figure shows the national estimated number of patients of all ages who received dispensed prescriptions for single-ingredient oxycodone from U.S. retail pharmacies. Shown by the blue patterned column, patients who received prescriptions for oxycodone IR increased from an estimated 3.6 million patients in 2013 to 4.6 million patients in 2018. During the same period, patients who received oxycodone ER prescriptions, shown by the dark solid column, decreased from 938 thousand patients in 2013 to 467 thousand patients in 2018.

This figure focuses on patient estimates for oxycodone ER by patient age. The vast majority of use was in adult patients as shown by the dotted orange line. We observed very limited pediatric utilization shown by the lines hugging the x-axis.

This figure shows a more focused look on pediatric utilization of oxycodone ER. Pediatric patients aged 11 to less than 17 years old, displayed by the solid green line, decreased from an estimated 2000 patients in 2013 to 400 patients in 2018. Very few patients aged less than 11 years old, represented by the dotted blue line, received the dispensed prescription for oxycodone ER. Please note the change in the y-axis.

In addition to oxycodone ER use, our analysis also assessed the pediatric use of single-ingredient oxycodone IR from 2013 through 2018. During this period, we observed an increase in oxycodone IR use for patients of all ages including pediatric patients.

Focusing on pediatric utilization of oxycodone IR, patients aged 11 to less than 17 years old, represented by the solid green line, increased from 35 thousand patients in 2013 to 68 thousand patients in 2018. Patients aged less than 11 years old, shown by the dotted blue line, increased from an estimated 27 thousand patients in 2013 to 63 thousand patients in 2018.

In terms of top prescribing specialties, based on dispensed prescription data, oxycodone ER prescriptions for patients aged less than 11 years old were written by primary care MDs such as family practice and internal medicine followed by pediatrics. Prescriptions for patients aged 11 to less than 17 years old were written by nurse practitioners and physician assistants including those in primary care and specialized fields. This group was followed by surgical specialties, a group we identified as any specialty related to surgery. Oxycodone IR prescriptions for patients aged less than 11 years old were written by otolaryngologists followed by surgical specialties. Prescriptions for patients aged 11 to less than 17 years old were written by surgical specialties followed by nurse practitioners and physician assistants.

We analyzed diagnoses associated with the use of single-ingredient oxycodone by using a proprietary database that provides national estimates for monthly surveys of office space physicians as previously explained by Dr. Ibrahim.

No data on diagnoses associated with single-ingredient oxycodone ER use in

pediatric patients was reported in the database due to possible low use of oxycodone ER. However, the top diagnoses that have been reported to be associated with oxycodone IR in pediatric patients aged 11 to less than 17 years old and less than 11 years old were for the management of sickle-cell disorders and dislocation of the joints at ankle, foot, and toe, respectively.

Our analyses had some limitations. Only outpatient utilization was assessed. No inpatient or mail-order data were included in the prescription analyses. However, the setting accounted for the majority of utilization. Diagnoses data are not necessarily linked to dispensed prescription data, rather the data presented were mentions of a drug at a physician's visit based on surveyed data of a sample of physicians. The diagnoses data were derived from surveys of office-based physicians and may not have captured prescribing patterns of physicians who practice in other settings such as hospice care or inpatient. The database does not include data from prescribers such as dentists and below practitioners.

Understanding the need for more granular data, FDA's approval of OxyContin in pediatric patients included post-marketing requirements, one of which is a drug utilization study to evaluate pediatric use in all care settings. The results will include the number of prescriptions and patients who received OxyContin; strength, dose, and dosing changes; patients' opioid tolerance statuses at the start of therapy; duration of therapy; and the indications or conditions associated with OxyContin dispensing.

This PMR was issued on August 2015 and the Protocol and Statistical Analysis Plan were finalized in May 2018. The sponsor continues to work to provide several data elements that are crucial in evaluating the OxyContin use patterns in pediatric patients. The final report is due in March 2020.

In summary, pediatric use of single-ingredient oxycodone ER remains low. Pediatric use of single-ingredient oxycodone IR appears to have increased over the examined

time. Oxycodone ER prescriptions for patients 11 to less than 17 years old were written by nurse practitioners and physician assistants, followed by surgical specialties. Our analysis using a physicians' survey database showed no data on diagnoses associated with single-ingredient oxycodone ER use in pediatric patients. Lastly, additional data requested under PMR are expected in March 2020. Dr. Patel will now present her findings from her pediatric safety review on OxyContin. Thank you.

DR. WADE: Dr. Patel, we welcome your presentation.

**PEDIATRIC FOCUSED SAFETY REVIEW: OXYCONTIN (OXYCODONE
HYDROCHLORIDE EXTENDED-RELEASE)**

DR. PATEL: Good afternoon. My name is Chaitali Patel. I'm a safety evaluator in the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology. Under the Food and Drug Administration Safety and Innovation Act, specifically the Best Pharmaceuticals for Children Act, BPCA, the agency reviews post-marketing adverse event data in the pediatric population after pediatric approval of a drug or a biological product. In accordance with BPCA today, I will discuss our analysis of post-marketing adverse event data specifically for OxyContin and oxycodone ER products from FDA's adverse event reporting system, otherwise known as FAERS database. The previous speaker, Dr. Bak, discussed the utilization patterns for oxycodone products in the pediatric population which focused on oxycodone extended-release products to provide context for our safety review.

First, I will provide some background drug information, discuss the relevant pediatric studies, and then move onto the safety review, and conclude with a summary which will include our findings and recommendations.

OxyContin was originally approved in December of 1995 and then reformulated

in April 2010 with inactive ingredients intended to make the tablet more difficult to manipulate or defeat the extended-release properties for misuse and abuse. The expanded indication to the pediatric population was approved August 13, 2015. The pediatric indication for OxyContin is for opioid-tolerant pediatric patients 11 years and older who are already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 milligrams per day of oxycodone or its equivalent for at least 2 days immediately preceding dosing with OxyContin. I have adult indication on this slide for your reference. OxyContin is available as oral tablets in the strengths listed here on this slide. The sponsor of OxyContin is Purdue Pharma.

OxyContin is also available as an authorized generic. An authorized generic drug is the same as the brand-name drug although it may have different markings or color and is marketed by subsidiaries of the brand by third parties under synonymous names. Whereas, a generic drug is a copy of the brand-name drug and is made by another company that requires FDA approval via an abbreviated new drug application or ANDA. Oxycodone extended release has been available as an authorized generic since 2014 and is currently supplied in all of the same strengths as OxyContin.

The OxyContin label includes a boxed warning addressing potential risks that are also relevant to the pediatric population. These will be important to remember while we discuss the findings from the FAERS cases. In brief, the risks include addiction, abuse, misuse, which can lead to overdose and death, serious life-threatening or fatal respiratory depression with use, accidental ingestion by children can result in a fatal overdose, exposure during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening.

Relevant pediatric studies -- to assess the safety of OxyContin in the pediatric population, the sponsor conducted an open-label study in patients ages 6 to less than 17 years of age. However, there was insufficient number of patients enrolled in ages less than 11 years and, therefore, insufficient information to assess safety in that population. Thereby, the approval for

OxyContin is in pediatric patients 11 years of age and older. In this study, patients were previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 milligrams per day of oxycodone or its equivalent on the 2 days immediately preceding dosing with OxyContin. The adverse events observed in the safety study included vomiting, nausea, headache, pyrexia, and constipation.

Expanded indication to the pediatric population was approved with post-marketing requirements: one of which is enhanced pharmacovigilance, and the second is the drug utilization study you heard Dr. Bak discuss in the last presentation.

Under the enhanced pharmacovigilance PMR, the sponsor is required to analyze post-marketing spontaneous adverse event reports in children less than 17 years of age for particular adverse events of interest which include respiratory depression, accidental injury, overdose, misuse, accidental exposure, and medication errors. Under this PMR, the risks highlighted in the boxed warning of the label were analyzed in the pediatric population. Data collection was initiated at approval through October 2018. Interim reports thus far have not revealed any new safety concerns, and the final report is currently under evaluation.

Now moving onto the safety review -- this slide illustrates our case selection process for the OxyContin reports retrieved from the FAERS database. First looking at the box in the middle, we retrieved 128 U.S. pediatric reports with a serious outcome. After reviewing all 128 reports -- now moving down to the box on the left -- we excluded two duplicates and an additional 37 reports of oxycodone that did not clearly specify OxyContin or an authorized generic product by stating extended-release or a synonym as a suspect product or in the narrative text, thereby, we kept for further discussion the remaining 89 FAERS cases of OxyContin or an authorized generic which included 13 fatal cases. Herein, I will refer to these cases of OxyContin and those of the authorized generics as OxyContin.

This graph illustrates the 89 cases by the year they were initially received by the

FDA and are stratified by age group. Eleven to less than 17 years represented, by the green dotted box, and the zero to less than 11 years is represented by the blue slanted line box.

Overall, we did not appreciate any notable trends in reporting to the FAERS database. We note that data from 2015 is for a partial year from the date of approval in the pediatric population.

This table presents the age, sex, and the reported source of the case report for the FAERS cases, again, stratified by age group. First, looking at ages 11 to less than 17 years, there is 1 case -- an 11-year-old -- and the remaining are in children above 12 years of age in both males and females. The majority of these cases originated from news media reports. In the ages 0 to less than 11 years, most of the cases were in children close to two years of age with a few children between 6 and 11 years of age. The majority of these cases were in male children and, again, mostly derived from news media reports.

This is a representative news media case to illustrate the breadth of case details: A 16-year-old female began taking OxyContin that was prescribed to her mother. According to the article, the patient became addicted and later started using heroin. This case did not provide any additional details including concomitant drugs, doses, route, frequency, details surrounding the event or clinical outcome from opioid addiction. News media cases generally lack granularity and limited our assessment.

DR. WADE: Pardon me, Dr. Patel. It's now 2:00 and this will close the open hearing. We'll now return to your presentation.

DR. PATEL: Thanks. The most frequently reported adverse events in ages 11 to less than 17 years are included on this slide. As such, not all adverse events are listed here, and a case may report more than one adverse event. Now, adverse events reported in the adolescent group include drug abuse, drug dependence -- of note, pieces of drug addiction are coded up to drug dependence -- and the other adverse events include drug overdose, malaise, and somnolence.

The most frequently reported adverse events in ages 0 to 11 years include accidental exposures and the specific adverse events are reported below, drug overdose, and neonatal opioid withdrawal syndrome or Nows.

The case outcomes among the 89 FAERS cases reviewed is presented in this table. There were 4 deaths in the 11 to less than 17-year age group, and these were described in the context of drug abuse and intentional overdose. There are several cases coded as life-threatening and/or requiring hospitalization, and majority of the remaining cases were reported as other serious. In the 0 to less than 11-year age group, there were 9 deaths, and these include one case of transplacental exposure to drugs including OxyContin which resulted in a stillbirth. One case in a ten-year-old child taking OxyContin for pain associated with cancer who died due to neoplasm progression. There were two cases of accidental exposure, and the remaining five cases were of drug overdose of which three cases are suspected to be from intentional administration by family members but prescribed or unprescribed use was not specified and the two remaining cases did not specify how the child obtained the OxyContin.

This table summarizes our evaluation of prescribed OxyContin use from the case series. Overall, there are 8 cases reporting prescribed use, all but one in ages 11 to less than 17 years. The lack of reported case details hampered our ability to assess opioid tolerance status as stated in the label. The adverse events reported in these cases include drug addiction or dependence in six cases, lack of effect in treating chronic debilitating pain in one case, and death due to neoplasm progression in one case.

Additionally, we suspect 5 cases may describe initial prescribed use for pain specified for a potential total of 13 cases of prescribed use, primarily in ages 11 to less than 17 years. All five of these cases reported developing drug addiction. In the remaining cases, as expected, depending on the age group, we see a divergence in exposure of pattern. Ages 11 to less than 17 years obtained the OxyContin from other sources whereas, exposure in ages 0 to

less than 11 years is primarily described as accidental exposures or transplacental exposure. And, in a few cases, it was given to a child by a close contact such as a family member or relative or a coach.

To further understand and characterize our cases, we evaluated the reported reason for use. This table shows there are 13 pain-related reasons for use including the 8 cases of prescribed use and the 5 cases suspected to be prescribed. Among the remaining 76 cases, the most frequently reported reason for use was drug abuse, misuse in ages 11 to less than 17 years and accidental exposure and transplacental exposures in ages 0 to less than 11 years. In fact, among these 76 cases, the reasons for use is representative of the adverse events reported. In ages 11 to less than 17 years, the most frequently reported adverse events are drug abuse and drug dependence/addiction and in ages 0 to less than 11 years are accidental exposures and drug overdoses. These adverse events correspond to the risks described in the OxyContin label most of which appear prominently in the boxed warning.

In summary, only appropriately 10 percent of the cases primarily in ages 11 to less than 17 mentioned OxyContin was prescribed to the child. Due to insufficiently reported case details, we are unable to assess opioid-tolerant status as defined in the label. Of note, this was also a limitation in our assessment of the interim reports of enhanced pharmacovigilance -- PMR. The majority of the 13 pediatric OxyContin cases evaluated with an outcome of death, the death was described in the context of drug abuse, drug overdose, or accidental exposure. The most frequently reported adverse events in ages 11 to less than 17 years are drug abuse and drug dependence or addiction, and in ages 0 to less than 11 years are drug overdose and accidental exposures. This particular finding underscores the need for continued education around environmental safety with opioid products.

No new safety signals were identified from our safety review or thus far from the enhanced pharmacovigilance PMR interim reports. However, based on the available data, FDA

recommends to continue ongoing monitoring of post-marketing safety reports and the completion of the PMRs. Thank you.

DR. WADE: Thank you for both of those presentations. We will now take clarifying questions for the presenters. Please remember to state your name, speak into the microphone. If you can, please direct questions to a specific presenter. We'll start with Dr. Havens.

DR. HAVENS: Thank you. Peter Havens. For the last presenter, is there a way to compare the deaths from OxyContin from abuse to other opioids? There's some data that suggest that OxyContin may have higher abuse potential than other marketed opioids. So, while this was just OxyContin, is there a way to make a comparison or have you done that otherwise?

DR. PATEL: So I'll begin by saying FAERS data have limitations, and, as I mentioned earlier, there's always a lack of granularity in these reports so comparing data from one drug to another drug is really hampered due to the data that we have in our database.

DR. STAFFA: This is Judy Staffa. I'd like to add to that, that when you're studying abuse, if you think back to Dr. Greene's presentation, many times the granularity to get down to a specific product is very challenging. It's just not available or not reported. So what you saw in her presentation was oxycodone which is, of course, available through a variety of different formulations. So it can be challenging to be able to discern particular products.

DR. HAVENS: Right. Does the FDA, in general, believe that oxycodone has higher abuse potential than similar products? There are papers published on that topic, and I'm just wondering how FDA feels about those papers which I recognize is kind of a broad question.

DR. STAFFA: This is Judy Staffa. With the epidemiologic data, it's challenging because when you're looking at abuse or misuse of an opioid, you're actually looking at the end result of a drug's abuse liability which is I think the point you might be getting at. But also, you're also looking at the availability because if someone is addicted, they will abuse whatever

they can get. And so it can be very challenging from epidemiologic data to be able to tease that out, and I'll defer to my colleagues in DAAAP to talk more about the actual abuse liability, the pharmacologic component.

DR. FIELDS: Right, so it's a very good question, and there's a contract with some researchers who are doing studies to determine the difference -- comparing drugs for their likeability and their euphoria, and we don't have the results of those yet, but they should be soon actually.

DR. HAVENS: Well, I'm looking here at a paper from 2012 by Wightman et al. that says, although three-fold more hydrocodone than oxycodone tablets are sold, the latter is proportionally responsible for much greater incidence of ED visits, arguing that the potential for abuse is higher even though the availability might be lower. So those kinds of studies are available and have been done and might speak to the issue of some of the reasons that, as you point out, oxycodone is said to have more euphoria than some comparators or greater likeability scores.

DR. FIELDS: I didn't speak to any specific drugs, but there is a difference among the drugs regarding their likeability. I think the evidence you point to is evidence but somewhat indirect where there are some researchers working on some direct studies to ascertain the differences, and it'll be interesting to see what the results of that study are.

DR. STAFFA: Right, this is Judy Staffa. Again, we do a lot of work of trying to understand differences between products and, as I mentioned, there's a lot of factors that influence that. So what we were trying to do for this advisory committee, we thought it would be useful background to provide what you saw in Dr. Greene's presentation which shows you the products -- I shouldn't say the products -- the actual moieties -- oxycodone and hydrocodone -- that are most often reported by adolescents or children as being abused and given the wide availability of those, we didn't think that was particularly surprising that that may be what they

can their hands on whether through prescriptions, through relatives and friends, or even illicitly.

DR. WADE: Great. I want to make sure we have time for everyone. Dr. Griffin.

DR. GRIFFIN: Marie Griffin. This is really interesting and gives us this perspective of a lot of the adverse events from non-prescribed, but I'm wondering if FDA's interested in looking at what the risks are for children who are prescribed the drugs by using some population-based data like fentanyl or something like that where you could actually look at children who are prescribed these drugs and do a longitudinal analysis rather than just have numerator data.

DR. STAFFA: This is Judy Staffa. Actually, we've thought a lot about that and there are a lot of challenges with studying these kinds of outcomes in administrative claims data. So much of these behaviors are covert activities, and they are often not picked up. Actually, through a series of required post-marketing studies, a number of the pharmaceutical manufacturers have actually tried to validate whether we can identify things like misuse and abuse in electronic medical record data, whether we can identify overdoses and signs of abuse in claims data. And it turns out that that's very challenging that you actually miss a lot. So we have been actively working to try to encourage the linkage of data sources to be able to improve the ability to do that with the idea that down the road perhaps that will be more possible.

DR. WADE: Dr. Meisel.

DR. MEISEL: Steve Meisel. I'm trying to wrap my head around something here that hopefully somebody from the Agency can help me with maybe Judy or somebody else. The vast majority of use of oxycodone is the immediate release, yet, as far as I can tell, immediate release is not approved in pediatrics, but the sustained release OxyContin is. Help me understand why the drug that's used for acute pain does not have approval but is mostly used, and that which is used for long-term chronic conditions which is less commonly used does have an approval. Why don't we have an approval for the immediate release in pediatrics?

DR. FIELDS: For many years, oxycodone was a marketed unapproved drug. What that means is it was marketed and used, but it was never approved by the FDA. Just recently, oxycodone tablets and oxycodone oral solution have been approved in the last few years, and there are PREA requirements outstanding at this time and the studies are ongoing, but we don't have the results yet.

DR. MEISEL: So I'm incorrect. There is a pediatric indication for immediate release?

DR. FIELDS: No, there are studies ongoing.

DR. MEISEL: Studies ongoing. It just seems odd to me that the Agency would approve an extended-release formulation of a product that doesn't have an approval for its regular use. That just seems like an odd regulatory pathway.

DR. FIELDS: It relates to how oxycodone was marketed for many years and the timing of the requirements. Just for clarification, the OxyContin language in the label was a result of what's called a written request, and I think Dr. Lloyd talked about that regulation and it was voluntary on the part of the company to complete those studies.

DR. WADE: Randi Oster.

MS. OSTER: Randi Oster, consumer representative. Could you please comment on the source of the FAERS data in terms of the percentage of the reports that came in from the doctors and patients versus the manufacturers? Because what I'm trying to get a sense of is, we have a lot of good data here. This data does count in terms of the after-market study where we have according on page 17, 13 serious outcomes of death, 5 life-threatening, and so I want to get a sense of how many reports are coming into the FAERS database and the source of them.

DR. MCANINCH: Just to clarify, is this specifically for the OxyContin cases that were reviewed?

MS. OSTER: It goes back to Dr. Patel's presentation of the data that she

collected, yes.

DR. MCANINCH: Okay. Of the 89 cases that we reviewed, all of the cases were submitted by the sponsor or from a pharmaceutical company.

MS. OSTER: Okay. And then to comment on that then, so the regular population you did not have any input, so there's a gap there.

DR. MCANINCH: That's correct. There were no direct reports, so we didn't get reports from consumers or health care professionals.

MS. OSTER: Thank you.

DR. WADE: Ms. Robotti.

MS. GADA: Excuse me. Hi. This is Neha Gada . I just wanted to add onto that. A patient can submit a report to the manufacturers who then have reporting requirements to submit those reports to us at FDA. So, in these case, as Dr. Patel mentioned, all of the report did come to us via the manufactures, but they could be from a variety of reporters including health care professionals or consumers. And then as Dr. Patel mentioned in this case series, many of the reports were from the news media.

MS. ROBOTTI: Hi. Susanne Robotti. So, still on the FAERS case, I'm struck by how many cases are excluded. FAERS is an important source of issues and yet nobody seems to be able to fill the forms out right or not many people. I've tried to fill out a form just as a practice, but, since I was lying, it figured me out, and I got bumped; I didn't have anything to actually to report.

Looking at the OxyContin cases, 39 were excluded and, apparently, they all came from the pharmaceutical company who doesn't know how to file them correctly, so we don't have the information. As I read in the backgrounder, there's a FAERS analysis there also for Opana. The numbers were lower substantially, under a hundred, and I can't remember. I can't look now and listen to what's going on, but something like 35 to 40 percent of those cases were

also dropped out because there wasn't enough follow-up information. These are important sources and indicators as you have said over and over. Why don't we have somebody call them up? It's 40 people that you could call and say, can you fill in the rest of the information? And, with Opana, it was even less, so it was 25 or so. You could follow up particularly if it's coming through the pharmaceutical company. That's even easier and, in fact, I don't know why everyone doesn't just report to the pharmaceutical company and let them do the hard work instead of the doctors doing it. Was that question clear? And I have a quick follow-up after that.

MS. GADA: Hi. This is Neha Gada. I just wanted to add on that in order for a report to be submitted to FAERS, there's only four elements that are required and that includes a patient identifier, drug event, and reporter information. So the quality of the information that we receive can vary, and I think you see that in the analysis that Dr. Patel completed. And so that's kind of makes it challenging to get the more clinically relevant information to meaningfully assess certain reports.

MS. ROBOTTI: I don't understand why you don't ask for the clinically relevant information either in the form itself very specifically or in follow-up. Is there any direct follow-up?

MS. GADA: The reporting requirements include that sponsors must conduct follow-up and reports that are considered to be serious from a regulatory standpoint or unlabeled. And so they do their due diligence at that point in time to conduct follow-up on these reports. And so those reports are considered to be expedited 15-day reports.

MS. ROBOTTI: Okay. I'll leave it, but the numbers just seem small enough to be much more informative. One hundred twenty-eight cases, 39 -- there's not enough information to be clinically helpful for you. I would think that it should be second questioned.

MS. GADA: Yeah, and there's a number of reports that come in I think when

sponsors may attempt follow-up, they may not actually -- they attempt follow-up, and it's up to the reporters to have the chance and opportunity to report the follow-up report back, so I think that's some of the limitations of our spontaneous data.

MS. ROBOTTI: Okay. This is a procedural question, and I don't know why it didn't occur to me before. Given that we're called here today to talk about labeling, and there's more post-marketing requirement information coming in from OxyContin and six months. I don't quite understand why we're called together today instead of in March of 2020 when there would be a robust, new post-marketing study. I'm not quite sure why we're looking at Opana instead of OxyContin. I'm not sure it's relevant, but I'm curious.

MS. WOODS: Hi. This is Corinne Woods (phonetic) with FDA. The report is due in March 2020. The last report that we got was actually over 400 pages, so it does take us quite some time to go through it and look at it, and then we discuss it internally. So, if we wanted to wait until then, we could, but it seems more important to do the labeling meeting now because of the timing for the OxyContin pediatric labeling.

DR. WADE: We have a standard recurring basis for review. Could you just clarify if the reason it's coming here today is that we are in the time frame where it is due for the recurring required review?

DR. MCCUNE: This is Susan McCune in FDA. I'm not totally sure I understood the question about the delay because I think maybe that's a little bit different question because that's a review of post-marketing commitments, and I would certainly defer to OSE and DAAAP about the post-marketing commitments. The reason why we're talking about the OxyContin safety review is part of the BPCA requirements that we need to look at the safety through FAERS safety utilization 18 months after a pediatric labeling change. And so that's what I talked about this morning when we don't see -- we are seeing -- so let me just back up by saying through BPCA and PREA, we are now upwards a little bit over 800 new pediatric labels.

So, as you can imagine, we're having more of these come up at 18 months to be able to look at the safety reviews. So we're doing a lot of safety reviews which is why I talked this morning about the web-posted reviews that are there where we don't see any new safety signals. And we wanted to bring OxyContin to the committee to review because of the use and the safety just to discuss it as we have done in the past with other BPCA mandated safety reviews. I think that a discussion of the post-marketing commitments would be something that would be separate from this conversation.

DR. STAFFA: Right. This is Judy Staffa. The PMRs were not on the same time schedule as the BPCA requirements, so there's a requirement for us to discuss drugs that have pediatric labeling. Most of the drugs that get pediatric labeling do not have post-marketing required studies. This one does, so we've mentioned it. We wanted you to be aware of it because they exist, but these studies are very challenging. We have asked them, on the utilization side at least, to go after data that we don't have, and we didn't have easy ways to tell them to access it. So it has taken a lot of time and energy for them to do this. So I would love to have those data to be able to discuss with you today, but they're doing as best they can. I would imagine that if anything comes up in those studies that we feel requires a public discussion, we would be bringing that back at that time.

DR. WADE: So I just want to alert people to the time. We can probably do one more question. We do want to get to the Opioid Analgesics: Translating Pediatric Study Results into Labeling -- the example that was given to us in our background materials before we go to break, but to remind people that after the break, there is an hour and a half time slot for further discussion and voting and clarifying questions. So we've been quite patient over here. I'm going to do one more question, and then we're going to move on to the last segment before break.

DR. KULLDORFF: Thank you. Martin Kulldorff. I thank you for your

informative presentations. I have a question. The reason why you're presenting this information on oxycodone is that (a) because you feel there's not sufficient safety information on oxymorphone, and then you feel that the oxycodone safety information can sort of inform about oxymorphone, like, interpolating from that, from oxycodone to oxymorphone? Or is it that you think that you want to contrast the safety in oxymorphone versus oxycodone and that the labeling of oxymorphone should be sort of influenced whether it is sort of safer or less safe than oxycodone?

DR. STAFFA: This is Judy Staffa. These are actually two completely separate topics but both topics that we felt were appropriate for these two committees to discuss. The first is the OxyContin. The standard BPCA safety review to discuss and decide whether anything further needs to be done and then the second topic is the topic that I think Dr. Lloyd is going to tee up which is about the use of PREA data in labeling using Opana IR as an example. So they're really not connected, those two topics. I apologize if we've confused you.

DR. KULLDORFF: You did confuse me, so thank you for clarifying that.

Thank you.

DR. WADE: That was an excellent segue actually into the next talk by Dr. Lloyd on Opioid Analgesics: Translating Pediatric Study Results into Labeling.

OPIOID ANALGESICS: TRANSLATING PEDIATRIC STUDY RESULTS INTO LABELING

DR. LLOYD: Okay. This is from my second presentation today. I'll be covering an example of the data from required pediatric studies that were conducted under PREA for an immediate release opioid analgesic.

So, as you recall from this morning or may not recall, PREA requires a pediatric

assessment for new drug applications under certain circumstances. There are many opioid analgesic drug products with outstanding PREA requirements. These studies are typically conducted post-approval, and the data are submitted as a supplement to the application. However, as we've noted, few opioid analgesics have pediatric labeling due to the many challenges associated with completing the studies, for example, too few patients available, parental concerns, ethical and logistical challenges with respect to study design, et cetera. However, when we do have the opportunity to review the pediatric data for an opioid analgesic, we consider the risks and benefits to the individual patient as well as with respect to the public health when evaluating the proposed pediatric labeling.

One recent example is Opana tablets which were approved in 2006. Opana tablets are an immediate-release formulation of oxymorphone that is distinct from the reformulated Opana ER, an extended-release formulation of oxymorphone, that was voluntarily removed from the market at the request of the FDA for serious risk related to abuse. Similar to other immediate-release opioids, Opana IR is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The PREA requirements for Opana IR are for an evaluation of PK, safety, and efficacy in birth to less than 2 years of age and then evaluation of PK and safety in 2 to 17. We received a supplement to the application this past December containing data from the required pediatric studies for the 2- to 17-year age group.

The Opana IR pediatric program utilized two formulations: First, the marketed Opana IR tablets formulation which was used for patients 12 to 17 years. The second was an oral solution that was used in the younger group that was specifically developed for the pediatric studies as sponsors are required to develop age-appropriate formulations for the required pediatric studies. And, although they're required to do so, they are not required to market those formulations. And, in this case, the sponsor does not intend to market the oral

solution formulation.

This is an overview of the Opana IR pediatric program. The company conducted three studies to support the pediatric program in 2 to 17 years. The first study, 101, was an open-label study conducted in healthy adults to establish bioequivalence between the marketed Opana IR tablet formulation and the oral solution formulation. The second study, 010, was an open-label PK and safety study conducted in 58 pediatric patients, 12 to 17 years of age, with acute postoperative pain. Single and multiple dosing was studied at the 5-, 10-, and 15-milligram dose levels. The third study, 302, was also an open-label PK and safety study, and it was conducted in 45 pediatric patients, 2 to 12 years of age, also with acute postoperative pain. This study evaluated the oral solution formulation using single and multiple doses, and although three doses were studied in the single-dose phase, only one dose was pursued in the multiple-dose phase at the recommendations of the DSM-V. Both of the two latter studies collected open-label, uncontrolled efficacy data.

The pharmacokinetic results are displayed here, and I don't plan on going through them line by line. But the clinical pharmacology review team has noted that it's reasonable to conclude that, based on these results, a 5-milligram single dose in 12 to 17-year-olds will provide similar oxymorphone exposures to that of a 5-milligram single dose in adults. Similarly, in the 2 to 6 and 6- to 12-year-old age groups, a dose between 0.05 milligrams per kilogram and 0.1 milligrams per kilogram -- for example, 0.075 milligrams per kilogram based on the fact that oxymorphone is dose-proportional in adults -- provides similar oxymorphone exposures to that of a 5-milligram single dose in adults.

Specifically, the pharmacokinetic analyses on the previous slide excluded 2 subjects in the 12 to 17 age group who received a single dose and had markedly elevated plasma levels of oxymorphone which are highlighted here. As you can see the C_{max} and AUC values are much higher for these subjects -- in many cases, many fold higher -- compared to the other

subjects in the group. The applicant investigated these subjects and could not find an obvious reason for why there were higher exposures in these two subjects. However, based on the available clinical and clinical pharmacology data -- which I will go over some of the clinical data later -- the second subject highlighted really appears to have had an erroneous result. However, the higher exposures in the first subject remain unexplained.

So displayed here is the patient disposition information for the study in 12 to 17-year-olds. There's a lot of information on this slide, but the thing that I want to draw your attention to is that a majority of patients from this study discontinued due to lack of efficacy. And it's about halfway down, you can see reasons for discontinuation and lack of efficacy. And you can see across all dose groups there were very high discontinuation frequencies due to lack of efficacy with about 57 percent of the overall population having discontinued for lack of efficacy.

So, although the pharmacokinetic analysis -- and this is some of what we discussed in the last presentation -- supports comparability of exposures between adults and pediatric patients two years of age and older which would allow for extrapolation of efficacy from the adult studies to this pediatric age group, these data call into question whether the doses studied are in fact the appropriate efficacious doses in pediatrics. There was a whole host of other efficacy data that were included in the application including pain intensity values, rescue medication use; however, those data did not inform the efficacy assessment.

So regarding safety, there were no deaths. There were seven serious adverse events that were largely related to the underlying condition for the surgical procedure, and they all resolved with targeted treatment. There were also five discontinuations due to adverse events that were mostly consistent with opioid effects, and they all resolved spontaneously.

Most patients experienced some kind of adverse event. As you can see here, approximately two-thirds of the pediatric patients experienced adverse events. And there were

more adverse events with multiple doses compared to the single doses as would be expected. The most common ones are listed here including nausea, pyrexia, constipation, vomiting, pruritus, and headache, edema, oxygen saturation decrease, muscle spasms, dizziness, and urinary retention. They were mostly consistent with the post-operative state and what is already known about opioid analgesics in, really, adults and pediatrics.

So based on all the data that were collected in the two pediatric studies, the sponsor has proposed pediatric labeling describing the clinical studies and safety information in the adverse event section of labeling, the pediatric use section of labeling, and the clinical study section of labeling. And, although the sponsor is not specifically seeking an indication in the pediatric population that was studied, they have proposed describing the pharmacokinetic results in Section 12 of the labeling with language describing the comparability of exposures between this pediatric population and adults.

So there's a couple of risk-benefit considerations that we've taken a look at in the context of this application. So, although the sponsor demonstrated comparability of exposures between adults and pediatric patients and the safety profile was generally consistent with that opioid analgesics, there are two main considerations that raise concern in this application: The first is that we saw a substantially higher exposure observed in 2 of the 24 patients which represented almost 10 percent of the population that received a single dose in the 12 to 17 age group. So, although this didn't affect the pharmacokinetic analysis, we have concerns about this finding from a safety perspective. The first patient was a 13-year-old female that received a single 5-milligram dose and completed the study. There were no adverse events reported for this patient, and her pain intensity scores generally trended down over the observation period. The second was a 14-year-old female that received a single 15-milligram dose. Three adverse events were reported for this patient, none of which were serious. Her pain scores were highly variable over the observation period, and she discontinued due to lack of efficacy despite having

markedly higher exposures in the samples which led in part to our conclusion that the results in this patient were probably erroneous in the absence of other explanations from this sponsor. Although neither of these patients experienced significant safety issues, these data raise concern for us over the potential for a higher than expected drug levels when this drug is introduced in the general pediatric population.

The second risk-benefit consideration of concern is that despite the fact that the PK data demonstrated comparability of exposures between adults and pediatric patients 2 years of age and older, there was a substantial number of patients that withdrew due to the lack of efficacy in the 12 to 17-year age group. These uncontrolled, open-label efficacy data suggest that the oxymorphone dose may have been too low, but the dosing for immediate release oxymorphone in adults is from older studies and is intended to serve as a starting point with dose titration as needed. So, obviously, a similar approach could be taken in pediatrics, but the issue here is that, if, in fact, titration to higher doses is needed in the pediatric population, we don't have any pediatric safety data at those higher doses.

I'd like to acknowledge the contributions of the clinical pharmacology and the clinical review teams in the content of this presentation. Thank you.

DR. WADE: Thank you for that. We have 15 minutes prior to break where we'll start with questions. Dr. McGough.

DR. MC GOUGH: Jim McGough, from UCLA. Two quick questions to the speaker.

DR. LLOYD: Yep.

DR. MC GOUGH: First of all, the study only had about a 50 percent response rate. I'm just curious in which this is really stunning to me. In adults, what's the typical -- how do they do in adult studies? Did they get 80 percent response, 90 percent response? Is there any comparison?

DR. LLOYD: This is Josh Lloyd, FDA. So is your question when you say response, do you mean in terms of discontinuation due to the lack of efficacy?

DR. MC GOUGH: Well, I'm just looking at it the other way. Given that it looks like only half the people stayed in, if we presume it was efficacious in there, that's only a 50 percent positive response or you could look at it either way. But compared to adult studies, do you get that number of people leaving for non-response?

DR. LLOYD: No, typically in the treatment group, we don't have that high of a discontinuation rate due to the lack of efficacy. Typically, we see a higher rate of discontinuation due to a lack of efficacy in the placebo group, but we don't see -- this was a much higher level than what we see in adults.

DR. MC GOUGH: Right. So these aren't like antidepressants that only work in 40 percent of people. So the second question is, do we know that the outcome measure, I guess through visual analog scale, has that been validated in this age group? Because, again, as a child psychologist, I would wonder if children cognitively have the capability of using -- it would be important to show that those kids can validly complete those scales because maybe the lack of efficacy is due to a lack of sensitivity of the assay basically.

DR. LLOYD: So the discontinuation due to lack of efficacy is not based on an assessment on any patient-reported outcome measure. These patients or the clinicians that were involved in their care requested that the patient be discontinued because they weren't achieving a response, and it's not necessarily based on a scale.

DR. MC GOUGH: So it's more of a global sense, probably.

DR. LLOYD: It's a global sense. But I will say that, in terms of scales, we used a variety of scales across the pediatric population with the visual analog scale or a numeric rating scale only reserved for the older patient groups, and then in younger age groups, there are other scales that are utilized such as the faces scale and then FLACC scale which assesses

crying consolability.

DR. MC GOUGH: Which should be valid.

DR. LLOYD: Right. So we use different scales across the different pediatric populations that are appropriate for that particular age group.

DR. MC GOUGH: And the last question, was there any -- did they have any clue about that one PK outlier -- genetic testing, renal functioning, liver functioning? I mean, was there any hint as to why they had that abnormal value or that outlier value?

DR. LLOYD: I'm going to ask our clinical pharmacology colleagues to address that, but, in short, we don't have any additional information about -- they were unable to identify a reason for that.

DR. YUN XU: Shu-Yun Xu, clinical pharmacology team leader. We communicate with the sponsor several times regarding what's the cause for that outlier and the sponsor could not find any reason. And, from our perspective, we also cannot find another reason. As for your question regarding the genetic reasons, oxymorphone's mainly metabolized by glucuronidation which is the same pathway for morphine. So, for that specific pathway, there no well-known polymorphism associated with that, so probably that's not -- it may not be an explanation for that.

DR. MCCUNE: Actually, I'm probably going to -- as long as these are just clarifying questions for Dr. Lloyd and then we're going to take a break, I have an overarching comment when we come back to start the committee discussion.

DR. WADE: That sounds great. So it's a reminder to us all that these are specifically clarifying questions for that presentation, and, when we come back from break, we will have the global overarching review prior to our specific questions. So Dr. Wilfond.

DR. WILFOND: Thank you. I was hoping you could clarify because maybe I missed it with regards to the intention of this example because as I understood it, they were not

asking for labeling. They were just going to have this additional information put onto the label. At the end, your last two slides are pretty sobering as far as potential challenges that would make me question using this drug, but yet, it was unclear to me whether the intention of the new labeling information was to discourage use or encourage use. I'm not sure if I understood that.

DR. LLOYD: This is Josh Lloyd, FDA. So you're asking about the intention of using the Opana example?

DR. WILFOND: Well, both the intents you used in the example and also what was the intention of the labeling -- new information was put to the label based upon this interaction. You described briefly the fact that there was questions about the safety data. There was questions about lack of efficacy -- the value of the efficacy. Those were put onto the labels. In your mind, was that meant as a way of trying to provide more data so that people would read that and therefore know to not use it? Is that what -- I'm trying to make sure I'm getting the point of this.

DR. LLOYD: That's proposed labeling from the sponsor. I really can't speak for their intentions. They're not here today to present.

DR. WILFOND: Okay.

DR. LLOYD: We're currently reviewing this application and reviewing the data and are trying to decide what would be appropriate for inclusion in labeling.

DR. WILFOND: I guess my question is more for the purp- -- I'm sorry for being so dense, but I mean, it's really more about -- and I realize you're right; it's the sponsor, not you, who has whatever their intentions are, but what do you see as the value of including information like this on the label?

DR. LLOYD: Well, I mean, that's kind of what we want to hear from you today. But, other than seeking an indication, there is potentially value for including information on the label about the pediatric use such as describing the pharmacokinetic data to describe that

concern because these drugs still, despite not having pediatric indications and labeling, are still used off-label. So it would be important to inform prescribers of these data so that they can be informed when they're using this drug product, for example, in an off-label manner.

DR. WADE: Dr. Hausman.

DR. HAUSMAN: Ethan Hausman from DPMH. The burden for what we put in the labeling when a pediatric supplement comes in is ultimately based on what the determination of the data are. Is effectiveness supported or not? What I did not hear from Dr. Lloyd -- I believe it's correct -- he didn't mention anything regarding whether there would be approval of the application or not.

And, just so everybody on the committee gets made aware of this, pediatric information from a completed PREA study will go into labeling in some fashion. The nature of the data that goes in is predicated upon what our conclusions of the effectiveness of the safety of the PK data. If in the hypothetical scenario of another drug where an application comes in which is entirely for pediatric use and it's approved, information is distributed throughout labeling. For a PREA study where an indication is not approved, some element of the study description will go into labeling, but it's necessarily a briefer description of the study. So absent any further comment on whether the application would be approvable or not which is up to the review division, that's sort of the range of the information that goes in. So, if it's a failed study - - again for a different drug -- if it were a failed study that was designed and executed properly but no effectiveness is established, a very short description would go into 8.4. And, for a different drug, if safety and effectiveness were clearly established, it would get distributed throughout labeling. So that's the spectrum, and that's all I really had to say on that issue.

DR. WADE: That was helpful and, again, this afternoon, when we come back from break, there is sufficient time to more further explore the global question which is that interaction between when PREA results get submitted and decisions are made for pediatric

information in the label.

So, in the last eight minutes that we have before break, we want to ask any data-specific questions of Dr. Lloyd, and I promise when we come back from break, we're going to continue this theme of how to most appropriately balance the data results and labeled information for children. So Dr. Meisel.

DR. MEISEL: Steve Meisel. Could you please put Slide 7 back up? The font on these handouts here are impossible. I have real difficulty with the second "outlier" patient here. First of all, I have a hard time with the term outlier, but, I mean, these are real numbers. As I understand it, the only reason that you're saying that this may be an erroneous result is that you can't figure it out. You have no other explanation. Is that right? Do we have any evidence that there was some problem with drawing the blood levels and they ran it wrong or there was something wrong with the machine or anything of those sorts? We're just saying, there appear to be no side effects, levels are really high, we can't figure it out, so maybe it's erroneous.

DR. YUN XU: Hi. This is Yun Xu, clin. pharm. team leader. We sent several requests to the sponsor and also we look at the reports the sponsor submit to us. So based on our interaction with the sponsor and also our review, we do not find any evidence to show that this issue was about any of the core measures. So I think that's the best we can have right now.

DR. MEISEL: So would it be equally a valid conclusion that this person had a true abnormally high blood level and got very lucky and didn't have a serious adverse event.

DR. YUN XU: Yeah, based on the current data, I think that's the best explanation we have.

DR. MEISEL: And that would also then mean that there are some people who have very high blood levels, and this drug isn't going to work, getting back to one of the earlier questions about efficacy, being lower in this population perhaps in adult populations.

DR. YUN XU: Josh.

DR. LLOYD: This is Josh Lloyd, FDA. Certainly, the higher exposure could be interpreted as -- because this patient didn't receive efficacy, because they discontinued due to lack of efficacy, and they didn't have any safety issues, it could be interpreted that they got lucky and also didn't achieve efficacy.

DR. WADE: Dr. Patrick, you had an immediate follow-up.

DR. PATRICK: Yes, I just had a quick point of clarification on some of the results. So the sponsor's asking for a label change for the liquid formulation for younger infants, younger children; however, I understand from the background information, they're not planning to market that at all. Is that right? I just want to make that piece is clear in terms of --

DR. LLOYD: This is Josh Lloyd, FDA. You're correct. They do not intend to market the oral solution formulation, and the labeling that they are proposing is a description of the studies and the study results using a formulation that they don't intend to market.

DR. PATRICK: Okay. Thank you.

DR. WADE: Dr. Flick.

DR. FLICK: I just want to comment on this patient. I think all of us who practice pediatrics recognize the difficulties sometimes in obtaining blood specimens in these children. I don't know how that specimen was obtained. But it's inconceivable to me that this represents a real sample, a real blood level. Again, it's inconceivable that the child would not have an adverse event related to that kind of blood level. So I just don't think that we should look any more deeply at that patient than to say that that's an erroneous value, and we shouldn't consider it beyond that. I mean, if somebody disagrees, I'm happy to think about it, but I just don't see how you could have a level like that without requiring airway support.

DR. WADE: Dr. Havens.

DR. HAVENS: Thank you. Just one quick question on the last slide called risk-benefit considerations where you say that data suggests a higher dose might be needed to

achieve efficacy in pediatric patients. The question was the adult population that was studied, how did that compare in terms of the requirement for prior opioid treatment at high doses compared to the pediatric population which I think in this study, wasn't it a requirement that you were on high doses for a while or is that the OxyContin study?

DR. LLOYD: This is Josh Lloyd, FDA. So that was the OxyContin study. The Opana study in children did not require prior opioid exposure and, actually, for adults similarly for the Opana IR which was approved, as I said, back in 2006, those studies for that in adults were also opioid naïve.

DR. HAVENS: So all these patients were opioid naïve, so this could not be an issue of prior opioid use and tolerance in this subject group.

DR. LLOYD: Right. These patients were not on opioids prior to the study.

DR. HAVENS: They were naïve.

DR. LLOYD: Yeah.

DR. HAVENS: Thank you.

DR. WADE: Great. So if we can keep our questions very specific in this final run. Dr. Griffin.

DR. GRIFFIN: I'm not sure how specific this is, but I guess the manufacturer did what FDA required under the 2009 guidance. So I'm just wondering if the 2009 guidance, are we going to discuss that and whether is FDA interested in whether we think that makes sense? And do these results make you question that guidance? And maybe we should discuss it after the break.

DR. LLOYD: This is Josh Lloyd, FDA. I don't think that these results call into question the overall approach because, as I pointed out in the presentation, the studies in adults where the exposures were demonstrated to be comparable to, those studies were really a starting point for the opioid dose and opioids are generally titrated to effect as a starting dose. And,

whereas in the kids, that might represent a similar approach that might be needed where that is the starting dose and then the dose is titrated to effect. But the issue that we have here is that then we don't have safety data at those higher doses to support the overall positive risk-benefit balance in this particular population.

DR. GRIFFIN: So you sort of can't get there from here.

DR. MCCUNE: I just had a question. When you were referring to the 2009 guidance, what guidance were you referring to? Sorry.

DR. GRIFFIN: The one Dr. Lloyd talked about in the --

DR. LLOYD: It was the 2009 public workshop where we discussed pediatric trial design and the approaches for extrapolation.

DR. MCCUNE: Oh, the public workshop. Oh, okay. Sorry.

DR. GRIFFIN: Yeah.

DR. MCCUNE: Yep. Thank you.

DR. FIELDS: That's not really a guidance in our lingo.

DR. LLOYD: It's a publication.

DR. WADE: Sarah Hoehn.

DR. HOEHN: Sarah Hoehn. I have one quick clarifying question for Chaitali Patel. When we reviewed all that prescription data, depending on which database you look at, some include dentists and some do not include dentists, and about 25 percent of what you presented were APNs and physician assistant. So I didn't know if the FDA could talk globally of people under the age of 18 getting narcotics. What percentage of them are prescribed by non-physicians? So your dentists and your APNs together, is it half? Is it a quarter? Like, if you combine the databases overall, what percentage are being prescribed by non-physicians?

DR. WADE: And you're referring to oxycodone?

DR. HOEHN: Yes.

DR. STAFFA: This is Judy Staffa. That actually was not in Dr. Patel's presentation; that was in Dr. Bak's presentation.

DR. BAK: Hello. This is Daniel Bak. Are you referring to the oxycodone ER prescriptions?

DR. HOEHN: I think so. I clearly messed up my page numbers. But I feel like there's been different databases and some include dentists, and some didn't, but it was when we were looking at the immediate-release oxycodone. It was the same slide that talked about what percentage where surgery subspecialties and they put all the surgery subspecialties together, and then 25 percent in addition to that were physician assistant and APNs and then it wasn't clear if that also included dentists. I'm just trying to get a sense of what's the scope of non-physicians prescribing opioids and oxycodone specifically to pediatric patients.

DR. BAK: Thank you for that question. According to the analysis that I did, dentists were not identified as one of the top prescribing specialties. The nurse practitioners and physician assistants that were one of the top prescribers of oxycodone IR among patients aged 11 to less than 17 years of age, this specialty or this group of practitioners can be listed under general practitioners or other specialties as well.

DR. STAFFA: This is Judy Staffa. Maybe I can clarify a little bit. In the prescription data, which is what this slide represents on the prescription, IQVIA actually links to the specialty that AMA has for that provider whoever is prescribing that, so that's why we can see the prescribers on a nationally projected sample of prescriptions. So what Dan's saying is that here, you're not seeing dentists pop up. They would here because they would be listed. The other source of information is the office space survey which is where we try to look for indication or what disease this child has that's being mentioned. That's the sample that does not have dentists; it only has medical providers in that sample so if that helps. So I think this is the relevant slide, so if you were going to see dentists, you would see them here and they're

showing you top, most frequent specialties.

DR. WADE: One last question.

DR. VOEPEL-LEWIS: Okay, this is Terri Voepel-Lewis for Dr. Lloyd. This sort of goes back to one of my previous questions about the adverse effects that kids that dropped out of the study of the Opana study the five discontinuations due to adverse events for sedation and CNS problems. I don't see those sedation, over sedation, or CNS problems listed in the sponsor's proposed labeling. So you mentioned before you thought that those were included, but it seems to me they excluded them from the labeling recommendation because there's nothing on excessive sedation or somnolence in their proposed labeling.

DR. LLOYD: This is Josh Lloyd, FDA. The sponsor's proposed labeling what I had said was they propose to include safety information from the studies in the adverse event section of the labeling. I didn't necessarily say they proposed to include the discontinuations.

DR. VOEPEL-LEWIS: Okay. So they did not include kids that were discontinued due to adverse events?

DR. LLOYD: I'd have to look at the proposed labeling.

DR. VOEPEL-LEWIS: I don't think they did because I looked at their proposed labeling, and they don't have anything on excessive sedation.

DR. LLOYD: I'd have to look at it to confirm that. In the presentation though, what I had said was that they proposed to include the safety information in those various sections of labeling.

DR. VOEPEL-LEWIS: Okay.

DR. LLOYD: If I recall correctly, in the adverse event section of labeling, they included tables about listing the common adverse events from each study.

DR. VOEPEL-LEWIS: Okay.

DR. WADE: With that, let's take a break. We're running a few minutes over, so

we'll come back in the room at 3:20, and that's when we'll start our general global discussion for the questions at hand.

[BREAK]

COMMITTEE DISCUSSION AND VOTE

DR. WADE: All right. If everyone could take their seats. So we will now proceed with the questions to the committee and the panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel and to remind the committee that we will be using paper ballots to cast our vote. There are two voting questions today and three discussion questions. The first question is here on the slide. Voting Question Number 1 --

DR. MCCUNE: Sorry. I was just wondering if I could kind of frame things before we --

DR. WADE: Oh, do you want to do that before?

DR. MCCUNE: Yeah, would that be okay?

DR. WADE: Yes.

DR. MCCUNE: Susan McCune, FDA. I apologize that we seemed to have confused folks, and I just kind of maybe want to clarify a little bit. And thank you for asking that question because that really helped. What we had thought we were going to do was provide a lot of background information in the morning that was useful for the global discussion and then have the two specific drug discussions in the afternoon. And I think that that was a little confusing because -- let me just walk you through kind of the drug development paradigm and kind of where BPCA and PREA kind of fit.

So you have a drug. It's being developed for an adult indication. You come in

with the data for your adult indication for your NDA or your BLA. And at the time, you have to have a pediatric study plan. And that pediatric study plan -- or you could do a written request under BPCA, but let's stick with PREA and the pediatric study plan. What we have seen is, in general, when you start your pediatric study plan, it takes 9 to 11 years to get pediatric data to come into the Agency. So you've done your adult studies. You've got the NDA where we start the pediatric study plan. Now we're 11 years out, and you've come in with information based on your PREA studies, and you get an indication. Let's just say you get labeling, and you get an indication for pediatric population. That then starts the clock for the BPCA safety review so that 18 months from then, we look at the FAERS data in terms of the safety of that product. And then that information is brought to the PAC either by presenting it to the PAC like we did today to the joint committee today for OxyContin or web posted like we did for the other 22 CDER, 5 CDRH, 4 CBER products that we posted online.

So we're asking you about two products that are at very different stages in development. So the first one that we're going to talk about first is really the OxyContin safety review and whether we need to do anything additional with that or continue our routine post-market safety monitoring along with the completion of those post-marketing studies that we talked about that will come in at a slightly future date. Then that one goes away, and then we kind of -- you -- focus on the discussion related to the Opana IR and the submission that came in based on their response to PREA studies, recognizing that it may have taken them quite a while to get that data so that the discussion about the study design may have been before we had a lot of information to support that study design, also recognizing that, as Dr. Lloyd said, there are a number of other products that are already in progress in terms of doing PREA studies. So there will be additional products that come in with information subsequently. Does that help a little? No. People are still looking confused. Sorry.

DR. WADE: I thought that was very clear.

DR. MCCUNE: Okay. Right.

DR. SLEEPER: Thank you for that explanation. This is Lynn Sleeper. So you mentioned for the one that's after 18 months, the OxyContin ER, and you said so you're asking us to know whether to continue the routine market or do something with that. What's that alternative when you say that?

DR. MCCUNE: Well, so what we have seen in the past associated with advisory committees where we have had discussions about safety issues, it generally is where a new safety signal has been presented, and a new safety signal potentially would be added to labeling. That is not something that was presented here. Let Dr. Hausman --

DR. HAUSMAN: Hi. Ethan Hausman from DPMH. In prior times, I was also over in the Division of Pharmacovigilance. So just as a background, with the routine post-market safety monitoring, that is a robust ongoing and active process. It's not, we didn't find anything. We put it in a filing cabinet, and we forget about it. The safety evaluators for different drug portfolios regularly go inside the data systems and they peruse for new events. So it's not a static periodic process that is activated every three years, for example. It's a regular ongoing thing, so when we say return to routine monitoring, that's return to an ongoing active process.

DR. SLEEPER: Okay. But if we say, we do not agree, what happens?

DR. HAUSMAN: If you did not agree, then it would be incumbent upon you to say why you do not agree and what you would recommend as an alternative if you have one.

MS. OSTER: Randi Oster. I just want to build on that. So the no answer is not that they're not -- you would still continue monitoring, but you would also have to explain what else we want you to do with monitoring.

DR. HAUSMAN: Correct.

DR. HAVENS: Yes, it could be enhanced monitoring, not just the routine.

MS. OSTER: Right. I just want to be clear. So no doesn't mean no, everything's fine. It's we -- okay, that's important.

DR. MCCUNE: I'm sorry. A no in terms of everything -- what does everything's fine mean? Sorry. Susan McCune, FDA. Sorry.

MS. OSTER: So I just want to be clear on the question, so yes means continue monitoring. No means there's additional research or issues that we have to bring up, but you would still continue monitoring it.

DR. MCCUNE: Yes, you would have to specify that. Yes.

DR. HOEHN: This is a follow-up. Sarah Hoehn. Can we specify if we think some words should be added to the label?

DR. STAFFA: This is Judy Staffa. I think you can recommend. If you see something in what we have shared with you that you think we need to do something beyond what we're proposing to do which is to continue as Dr. Hausman said. Our adverse events surveillance, completing the drug utilization studies, continuing to look at the use of the product. If you think we need to do anything more than that, this would be the time to tell us that and we can take that back.

DR. MCCUNE: And this is Susan McCune. For OxyContin, this is related to the safety review of OxyContin.

DR. STAFFA: Correct.

DR. WADE: And we would just say in our background material that's why we were given the label in to align with the safety review that was performed and conducted. Terri.

DR. VOEPEL-LEWIS: This is Terri Voepel-Lewis. It would help me if the labels were up on the screen so that when we discuss them, we could see what the current labeling is and exactly what we're asked to vote on. I know I'll refer to the page number because I can't find it.

DR. MCCUNE: This is Susan McCune, FDA. Part of the problem is the label is 25 pages long. Sorry.

DR. VOEPEL-LEWIS: Even the main point. You know, like that main -- I understand the label is really long because I read a lot of that, but it would be nice to at least see or refer to the page where it starts because I had taken notes and would like to get back to that.

DR. MCCUNE: Okay. Let me see what we can do.

DR. WADE: And while we're looking for that reference, I just want to alert people if you keep scrolling through today's agenda, the two voting questions and the three discussion questions are at the end of the agenda packet if that helps you. I think we could either show a slide of the black box warning that was reviewed, or we could just alert to the page in the background briefing documents.

DR. HAVENS: The OxyContin label was sent as a separate document completely, so it's in the file as a whole PDF.

DR. MCCUNE: We'll have it up in a few minutes.

DR. HAVENS: The oxymorphone was sent as a part of the backgrounder and there are the parts for potential change are identified in red. That was Peter Havens.

DR. MCCUNE: This is Susan McCune. We'll have the OxyContin front page up in a minute.

DR. FLICK: Randall Flick, Mayo Clinic. Again, I just want to be clear here; we're displaying the labeling information for OxyContin but the question to the committee is not about labeling for OxyContin; it's about ongoing safety evaluation. And the question was raised, if the committee were to say no, then you would come back to us and say, why? And we would say why we think it's no and that would have to inform your discussions with the sponsor. You'd have to go back to the sponsor and say the committee -- or if you agreed with the advisory committee -- you would go back to the sponsor and say, the advisory committee

recommended X, Y, or Z. We agree with them. We want you to do X, Y, or Z. That's the way this would work.

DR. HAUSMAN: Hi. Ethan Hausman. From the way the question is being presented to the committee, no means you disagree with going back to regular routine monitoring and you have an alternative. Yes can mean, yes, go back to ongoing monitoring, and, if you have an additional comment, you would say, however, we also recommend X or Y or Z.

MS. OSTER: No, that's not clear. That's not a clear question. That doesn't make sense because --

DR. HAUSMAN: Okay. Let me try this one more time.

MS. OSTER: Try it again because that doesn't make sense.

DR. HOEHN: I think there's a way they both make sense. Sorry. This isn't working. I guess we've talked too much.

DR. HAUSMAN: Yes.

MS. OSTER: We can't --

DR. HOEHN: It's not working.

MS. OSTER: Try it again. Got it. Here.

DR. HOEHN: Sorry. Sorry. Sorry. I'm just saying I think listening to -- this is Sarah Hoehn -- Randi and listening to Dr. Hausman, to me, there's ways that all of the above can be true. So I think if we reviewed the OxyContin data, and we do not have new, fresh safety concerns that we would want an enhanced level of monitoring, we could say we agree with continuing current level of monitoring. However, I, myself, could say that I have a concern from a public health perspective that with any long-acting narcotic, we should be proposing a consideration of co-prescribing of Naloxone which wouldn't be dictating a practice of medicine but merely a suggestion but a suggestion from the FDA or a suggestion that would

prompt the pharmacists or prompt the APN or prompt the dentist or prompt anybody to say, gosh, do I have concerns? And, if I have concerns, maybe I should also give them Naloxone which doesn't mean I have to vote no, but I could vote yes and then have a yes 1A proposal if that's what you're saying, right. If we wanted to say that, we could.

DR. MCCUNE: So this is Susan McCune. I think we're confusing labeling discussions that you all are going to be having in the discussion questions in the second voting question. With the first question which is what I told you that essentially after the pediatric labeling is done, then 18 months after the drug is on the market, we do the safety review. The OxyContin question is about the safety review and any concerns that you have about the safety data that were presented associated with OxyContin, not having anything to do with Opana IR if that helps to clarify.

DR. WADE: Right. And I would just say in other examples, not today, sometimes there are safety reviews that come up with a new safety signal that do not currently exist in the label. And, in light of a new safety signal, there could be a different recommendation put before the committee that goes beyond the ongoing pharmacovigilance and asks further exploration of a new safety signal. And that's why we have this cross talk between the safety review that was performed and the safety information that already exists in the label because there always is a possibility in pediatrics, particularly, that on ongoing surveillance new signals may come forth that were not previously recognized in an adult population. And that's where this mechanism of review and bringing to this pediatric committee and safety committee has been helpful.

In this specific scenario, the question being posed to us is, in light of the safety review information that was presented in our background and presented in presentation, ongoing pharmacovigilance as is already happening will continue but no new safety discoveries were elucidated that would put us on a different route. Is that helpful?

DR. VOEPEL-LEWIS: So the thing that we're voting on first is there are two parts: one says no new safety signals were identified. If we disagree with that, we can vote no. And then the ongoing continued safety monitoring, we could agree with that, but we could disagree with the first part and vote no on this.

DR. WADE: Typically, the recommendation for -- go ahead, Suzie.

DR. MCCUNE: Sorry, this is Suzie McCune. Just to clarify, this is OxyContin. This is not the Opana IR, but yes, the no new safety signals were identified was an FDA assessment so, yes, you could say no to that as well as a recommendation for something different than what we had recommended.

DR. VOEPEL-LEWIS: So, to clarify a yes for voting question number one means that you would agree that no new safety signals were identified, and ongoing routine post-marketing safety monitoring continue. A vote no you would then clarify as we go around the table to announce our vote. You would clarify where your disagreement is. Is it with that you believe there is a new safety signal? And, with that, you have a new recommendation.

DR. WILFOND: Can I ask one clarifying question?

DR. WADE: Yes.

DR. WILFOND: If it turns out that the cumulative -- I mean, what happens with all those nos? Does that turn into a new recommendation that we vote on or those are just we just have to make one decision today and then those records of the reasons why people made different decisions. I just want to understand that.

DR. WADE: Yeah, Kelly Wade. So all of our votes are recorded on -- voting number one is on this pink sheet of paper. We will hand them in. They're all formally reported on paper. We will then go around the room and everyone will have an opportunity into the microphone for the transcript to report their vote. And, if you feel that you would like to add clarification to why you voted the way you're voting, that will be entered into the transcript and

at the end of the vote, we have offered a committee's worth of opinion. I see a remaining question over here. Dr. Lesar.

DR. LESAR: Timothy Lesar. I just had a question. What role we're supposed to be considered the PMR study that's upcoming in terms of our vote that is there were lots of questions about the data we presented which I assume is the usual ongoing monitoring. So, if we say, yes, I think we can do that pending this PMR study, how much confidence will we have that PMR might answer some of the questions that the committee has address today?

DR. WADE: The reference is to the future PMR study report that's expected. I think we would assume that that is going to be submitted, formally reviewed, and barring the findings of the review may or may not be brought to this committee.

DR. STAFFA: This is Judy Staffa. Yes, as it says in there, part of, in this instance with OxyContin, part of the ongoing routine post-market review which normally for many drugs only includes our own review of FAERS data and utilization review, for this drug, it also includes those post-marketing required studies. We will be bringing those to completion, and I think in the presentations you saw, what additional information will be gathered in those studies.

DR. WADE: Dr. Turer.

DR. TURER: My question has to do with there were the drug overdoses, the six drug overdoses, in the children 0 to less than 11 years. And, in looking at the indication for the drug, it's in an opioid-tolerant patient who can tolerate 20 milligrams of oxycodone. Well, if you calculate an average size of an eight-year-old boy or an eight-year-old girl, it's around 60 pounds which is around 27 kilos or so, which when I do the dose calculation, it would only be about 2.7 milligrams twice a day but yet the smallest dose of OxyContin is, I believe, ten milligrams. It doesn't come as like an extended release, any sort of suspension, or et cetera. So, in considering with the extrapolation requiring the dosage formulation is fitting for the

population, I wonder -- and this probably was a previous discussion if there was a smaller dose -
- is it possible that some of the overdose events could be averted if there was a more pediatric
friendly formulation.

DR. PATEL: Hi. This is Chaitali Patel. The drug overdoses that you're referring to were -- the OxyContin exposure wasn't clearly stated in the narrative how the patient obtained it, and that's why these are characterized as drug overdoses. They exhibited signs and symptoms of overdose. As far as the dose, the dose wasn't clearly stated as to what dose the patient received. And these were in cases of prescribed -- we don't know if these were cases of prescribed use.

DR. FIELDS: Just to add to that, the lowest available dose of OxyContin is ten milligrams.

DR. VOEPEL-LEWIS: I just want to clarify what the ongoing routine post-market safety monitoring along with completion of post-marketing required studies specifically entails. It's the pharmaceutical company provides you ongoing data from their surveillance which is self-reported from physicians who report to the company, I assume, or people that report to the company. It doesn't include rigorous studies in this age group like post-marketing Phase 4 studies.

DR. STAFFA: This is Judy Staffa. So there's two different post-marketing requirements that the sponsor's pursuing: one is reviewing their adverse event reports that come to their attention in addition, and then our folks also do a review because, as was noted previously, we receive reports from the sponsor, but we may also receive direct reports.

DR. VOEPEL-LEWIS: And from the news media it says --

DR. STAFFA: Correct. The second study is the drug utilization study. That's where they're going out. Now, we have access to proprietary data as you've heard presented today. But what we've asked them to do goes far beyond what we are able to access, so they are

going out into a series of different places throughout the country and collecting information beyond what we can do on opioid tolerance of patients indication, age distribution, dosing, et cetera and that was described in one of the presentations, so those are the studies that we'll be continuing until completion. Does that make sense?

DR. VOEPEL-LEWIS: And they do those in teens.

DR. STAFFA: This is in children.

DR. VOEPEL-LEWIS: So they look at tolerance, dependence, and addiction, and opioid use disorder and teens who may be more vulnerable to those problems.

DR. STAFFA: What they'll be doing is looking at utilization in those age groups and understanding it. They will be looking at adverse event reports for reports of abuse, addiction, overdose, death, et cetera.

DR. WADE: Dr. Patrick.

DR. PATRICK: Relevant to this question, I just wanted to say, since we're talking about safety signals, but it's actually pretty encouraging that we see a decrease in prescribing after the indication. And one of the only things that I see is a little bit odd is whose prescribing, and I think just for the record because this is going to be in the data that's coming out soon. When we sort of initially had these conversations like three years ago and the fact that we had -- this is specifically for kids with chronic illness, kids in palliative care situations and the prescribers at least for the ERs think that they don't seem to -- they're NPs and primary care doctors. And so as we sort of see the data that comes out in the spring, it will be really interesting to see where that's coming from.

My sort of overall view of this question because I think that's what we're supposed to be commenting on is that I don't see any other safety signals that are particularly concerning. And, in fact, I see kind of reassuring data in terms of that we're not seeing the massive increase in use and adverse effects.

DR. STAFFA: This is Judy Staffa. That's correct in the utilization study, as I mentioned, in the IQVIA data, which are the national data, we have national coverage, but we don't have a lot of detail. So the goal of these utilization studies was to actually dig down and understand more the prescribers, the indications, in a more thorough way.

DR. FLICK: Just a quick comment that applies to this and others, the NP's and PAs don't necessarily suggest that those are primary care providers. In fact, I would think the majority of them are not primary care providers. They're NPs and PAs who work for a surgeon in all likelihood, and they're prescribing under the guidance of that surgeon.

DR. PATRICK: Just to clarify, I think the first category was primary care, the second category was NPs. That's what I was commenting on in terms of the lack of detail.

DR. WADE: And can someone from Med Safety, Drug Safety, or Dr. Hausman comment on whether or not a literature review is also part of this ongoing pharmacovigilance? It seems like, in the past, we also have had a review of the literature for other safety signals that would not have been foreseen. I just wanted to hear if those were still happening.

DR. HAUSMAN: Dr. Ethan Hausman, from DPMH. Yeah, a literature review is part and parcel of the pediatric focused safety review.

DR. WADE: So just information for our newer members of the committee that in addition to what we have heard today and access to data that is available to the FDA to provide these search for safety signals, there is also a parallel approach reviewing the literature base and the peer-reviewed domain.

So, if there are not further clarifying questions to this specific question, we can now open the question I think for vote. Yes?

MS. BRILL: Mm-hmm.

DR. WADE: Here we go. If there's no further discussion on this question, we will now begin the voting process. Again, it is the pink sheet of paper. We will begin using

paper ballots for this meeting. Voting Question Number 1 is printed on pink paper. You will have sixty seconds to vote. After everyone has completed their vote, members of the Office of Pediatric Therapeutics will be collecting the ballot. The vote will then be displayed on the screen and the Designated Federal Officer Marieann Brill will read the vote from the screen into the record. And next we will go around the room and everyone who voted will state their name and vote into the record. If you wish, you can also state the reason why you voted as you did. This will open voting.

Times up. They'll now collect our voting sheets.

MS. BRILL: For the record, the results are 20 yes, 5 no, 0 abstain.

DR. WADE: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and, if you want to, you can state the reason why you voted as you did into the record. I think we'll start this announcement -- I was going to start it over here if that's not too confusing with Ms. Celento.

MS. CELENTO: Sure. Yes, Amy Celento. I voted yes.

MS. ROBOTTI: Susanne Robotti. I voted no. The FAERS data is a major indicator that we have, and yet about 30 percent of the reports are lost because there's no follow up because they're incomplete. I believe the information given to the FDA through the pharmaceutical company is deficient, and it would be too easy to drop a bad report. I don't know what the oversight is. I'm sure it's very good, but I'm not confident. I also think that long-term studies for a product like an analgesic with this process with this method of operation should be -- long term studies should be added to the review process.

MS. OSTER: Randi Oster, consumer representative. I voted no. I voted no based on the results of the discussion today specifically Dr. Foster this morning said we need rigorous studies as we, as a team, looked at the studies, we came to the conclusion that the sample sizes were small. The second doctor that spoke was Dr. Greene, and he said there were

no studies done on addiction. The question was safety. Addiction is part of safety, and we clearly were presented today that that has not been happening. The third was Dr. Patel, and she talked about six overdoses, and there wasn't a clear reason why. And so, therefore, the question of no new safety indicators I could not support, but it is important to do continuing ongoing monitoring. I'm not against that. The question -- it's important that I just believe we have to do both and so the answer was no.

DR. WILFOND: My answer was yes.

DR. WADE: Just state your name and the vote.

DR. WILFOND: I'm sorry. Sorry about that. I always forget to do that. This is Ben Wilfond. My answer's no.

DR. WADE: You voted yes.

DR. WILFOND: Oh.

MS. OSTER: I convinced you. Can he turn around?

DR. WILFOND: I just got confused. I'll try it one more time. This is Ben Wilfond. My answer is yes.

DR. GRIFFIN: Marie Griffin. I voted yes.

DR. FLICK: Randall Flick. I voted yes.

DR. PATRICK: Stephen Patrick. Yes.

DR. ANNE: Premchand Anne. Yes.

DR. HAVENS: Peter Havens. I voted no hoping for guided studies to see if OxyContin has higher abuse potential than comparator agents thinking that there are many places in the label that that information could be placed. And it goes to a very specific large part of what the presentations have been about today as we look at public health problems associated with specific drugs.

DR. SAYEJ: Wael Sayej. I voted yes based on the question that's being asked;

however, I do have a lot of concerns. The fact that there are many outstanding PREA requirements is concerning to me, and I think they should be enforced by the FDA. I think there need to be better checks and balances on these medications once they're dispensed. Who's in charge? Is a teenager going to be in charge of a bottle of OxyContin or the parent is going to be in charge of overseeing the medication? And what happens once they're done with it? The disposal question comes into mind here.

I certainly agree with the recommendation of possibly prescribing something like Narcan for patients who are old enough to -- or high-risk patients who might need this. It is, however, very reassuring to me to see that the prescription numbers are going down overall, not necessarily for OxyContin but overall, which is reassuring that our prescribing habits are changing which is extremely important in the general public.

DR. CALLAHAN: David Callahan. I voted yes.

DR. TURER: Christy Turer. I voted no in part I think prescriptions went down a little bit because OxyContin changed its formulation. The drug became much more expensive, and that was about 2015. I can't prove that, but the thing that I think is really telling, I agree, that there's a huge safety signal. It may be on the label that it can cause addiction, nevertheless, I think we are facing a major opioid epidemic, and the numbers for drug abuse, dependence, overdose are very concerning. And so I'd really like to see at the very least a REMS on these that requires drug testing. I don't know why primary care providers would have any reason to prescribe these. That's very odd to me. It makes me wonder are those pill mills. Are those -- you know, we've seen some of those. Why are primary care providers prescribing OxyContin? That does not make any sense to me. So I think there just needs to be something more than simply ongoing monitoring to drive those numbers down in terms of the abuse.

DR. HOEHN: Sarah Hoehn. I voted yes reluctantly. So I voted yes because I don't think there's actually any concerning safety signals specific to OxyContin based on what

we reviewed today. I do think we're in the middle of a public health crisis with both suicide, mental health issues, addiction, all these different things. And I did put two notes on my yes which is that I do think from a policy perspective, the FDA should consider restricting prescriptions either not primary care, not dentists, I mean different things. So I think there should be some thought to whether or not these long-acting narcotics and long-acting opioids should be restricted.

Then the second is I think in the label where it says, Area 5.2 the risk evaluation mitigation strategies, I think we should have a consideration of whether or not we should consider recommending co-prescription of Naloxone as a specific risk evaluation mitigation giving how long acting OxyContin is.

DR. LESAR: Timothy Lesar. I voted no. My main concerns were that the discussion today would lead me to believe we don't know enough about how this drug is being used to help us design a better label which may help us use this drug more effectively and more safely. So my concern wasn't so much that there wasn't any safety signals so much as that there's inadequate information to understand how to better label this drug to promote better use to understand what's going on. I do hope the PMR will answer many of those questions, but I'm not all that confident. And, again, I think that from an editorial standpoint, I believe the package insert could be vastly improved as a tool for prescribers and possibly it could be best informed through better information through better data.

DR. VOEPEL-LEWIS: Terri Voepel-Lewis. I voted yes reluctantly as well. But because I've heard how the surveillance proceeds, I'm hopeful that the surveillance will be very rigorous and vigilant, and that the FDA will consider any new information in terms of ongoing approval for this drug for this age group. I do think that there are safety concerns, however, that were raised today. Hopefully, the surveillance will catch some of that, but I also disagree with the labeling as Timothy did as it currently is.

DR. MEISEL: Steve Meisel. I voted yes and some of you in meetings like this with me before has heard me say that the FDA needs to go to the question writing 101 school because the way these questions are worded creates a lot of confusion and can lead to answers that are not compatible with what people are thinking. There were no new safety signals that I saw that the FDA identified, and I do agree that continuous ongoing routine monitoring is necessary. So answering the question to me it's an obvious yes. Does that mean that this drug is safe? No. Does it mean that it's always used properly? No. Does it mean that there aren't other opportunities to improve risk or lower the risks going forward? Of course, there are, but that wasn't the question posed to us. The question was based on the safety review, and I saw no new signals, and I saw some positive signs in terms of utilization so that explains my vote of yes.

DR. PERRONE: Hi. I'm Jeanmarie Perrone. I voted yes, however, with the caveat that I think we continue monitoring the absence of finding new safety signals does not mean that they don't exist, and I think we should increase the rigor of that monitoring including specific surveillance investigating all pediatric opioid deaths for the source of the opioid which is not currently done in a systematic way.

DR. MCGOUGH: Jim McGough. I voted yes.

DR. ORTIZ-AGUAYO: Roberto Ortiz. I voted yes.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes.

DR. CZAJA: Angela Czaja. I voted yes.

DR. HABEL: Lori Habel. I voted yes.

DR. KULLDORFF: Martin Kulldorff. Yes.

DR. HOLUBKOV: Rich Holubkov. I voted yes. I think the safety signals are -- no new signals were identified. The risks are known. The monitoring system seems like it works. I agree the risks are gray, but the signals that the safety signals are known, and the

system seems to be working for that.

DR. SLEEPER: Lynn Sleeper. I voted yes.

DR. WADE: Thank you, everyone. We will now continue with the questions to the committee and panel discussion. So the next question for discussion -- again, these are written in the back of the agenda -- is acknowledging that pediatric patients have a need for adequate pain management that includes the use of opioids when appropriate. To accomplish this, product labeling should include appropriate pharmacokinetics, safety, and dosing information from clinical studies. Discuss the appropriate strategies for describing the results of studies conducted under PREA in labeling while taking into consideration the public health considerations of opioid misuse and abuse.

So, for these next three questions, the Opana IR information was given to us to facilitate this discussion. I think in this first question we have here deals with taking the information we get from PREA-required studies into the pediatric label.

DR. SLEEPER: Could I ask a housekeeping question to this? Lynn Sleeper. So I understand discussing number 2 which is discussion, but it seems to me that number 3 and 4 discussion questions are completely conditional on voting yes for number 5. So I was wondering why those discussion points didn't come after the vote because if the vote turns out to be no, then 3 and 4 seem to be moot because they're worded to be very specific to the data from the Opana IR.

DR. WADE: I think the discussion is desirable regardless of the vote at the end, and so, as a way to facilitate discussion without a commitment to voting one way or another, the discussion points are brought up front.

DR. WADE: Dr. McGough.

DR. MCGOUGH: Jim McGough. Is it just to help inform at least my understanding of all three questions, question to the FDA, what are the implications of having

data from non-indicated populations on the label because, from my read of it, to me, it's kind of mixing things up. It's like you have -- I'm a child psychiatrist. I prescribe off label all the time, but it's kind of on my own back. But, if I go to the PDR and it says not indicated in children under 12, but then I see PK data for kids who are six, then I say to myself, well, they're kind of telling me here that maybe I need to go higher on my dose to get an effect. I mean, I just wonder what the view of the Agency is towards including data from populations for which the label's not indicated, and are there negative ramifications to that? Did you ever get into difficulties? Because to me that's telling me as a practitioner that, oh, well it says not indicated for kids but they're also telling me I have to go higher because they don't get affected with the regular doses? That's real problematic from my view. So what is the view of the agency?

DR. HAUSMAN: Ethan Hausman. I'm going to defer to the review division on that one. DPMH has particular recommendations that we share with the divisions, but I think it's still predicated upon what their conclusions of the data are. And they've been descriptive today, but I don't think they've made particular recommendations yet. So I'll defer to the division.

DR. ALEXANDER: This is John Alexander. I'm from DPMH. I'm one of the pediatricians. And I will add a little bit with regards to the response. We do carefully consider the information that we put in, so our tendency -- and this goes back a long time and includes for adults as well -- that we don't put in necessarily information to the labeling that we think implies a claim or implies a specific use. So, with pediatrics, one of the things that we've changed in terms of the approach -- and, again, this goes back the 20 years that we've been adding pediatric labeling and pediatric requirements -- was to try and make sure that information, positive or negative, got conveyed. So that does mean that when we think that a drug can be used, we will often then convey, in labeling, that safety and effectiveness have been established, that the drug is indicated for whatever age group we think that drug is useful for,

and then we will include the information on the dose that we think is recommended in that age group, the clinical pharmacology data to let people know sort of what the exposures are that we see in kids in those age groups for which it's indicated. When it comes to a drug that we think is not recommended for use -- so the studies were either failed or there was some safety issue -- then we usually limit the amount of information that we convey with regards to anything that sort of implies a dose that we don't think is appropriate to be used. And we also will then convey what are the safety concerns or what are the issues that sort of prevented us from approving it even if it's -- they did a study; it was too small for us to be able to conclude anything with regards to how well the drug would work in this situation.

DR. WADE: Dr. Havens.

DR. HAVENS: Peter Havens. First of all, the question of the utility of the FDA product label was raised earlier today in somewhat of a negative light. And can I just say I think the FDA product label was a great -- one of the greatest things in the world. You standardized them. You know where to go and where to find what you want. Section 8, you can get pediatric data. The question of what doesn't or does get published in other places can get published in the product label. Somebody spoke and said, nobody ever reads product labels. In fact, some people read them a lot, all the way through, and from my perspective -- so this question that we are supposed to be discussing about, is there a need to include stuff in the product label? Absolutely. Thinking about the drugs we're looking at; you can look at 5.1 or 9.2 talking about the abuse issues; 6.2 has post-marketing places where you can go; 8.4 has the pediatric use. You should not publish what those guys sent you to publish; that's crazy. But it's where you could put in that 58 percent of people stopped because it didn't seem to work. So, to get to the question -- but then you guys said in your presentation that .75 milligram per kilogram in children gives you bioequivalence of 5 milligrams in adults. That's useful information. Whether or not it works should be put into -- questions about whether or not it worked should

be put into 8.4 in pediatric use. So the labels are great. They serve an enormous purpose for -- and I think this a perfect example. The company is not going for an FDA indication, but a lot of people are using it to say that this is the bioequivalent dose and studies that were done did not show benefit of that dose. There's a lot of information there. I would not allow them to say that safety and benefit were shown at ages 2 to 11 and part of the difference between the hydroxymorphone and the OxyContin were -- the OxyContin, there's a table that they have which clearly had statistically significantly different rates of using other narcotics in the placebo versus other groups. So I think there are data that allow you to go for an indication, but the data that were presented for this drug, Opana, do not justify a new pediatrics indication. But it's data that should not be lost, and the greatest place to put it is in the label. Thanks.

DR. WADE: Dr. Callahan.

DR. CALLAHAN: David Callahan. I'm a child neurologist. And my example would be levetiracetam or Kepra. It's not indicated. It's used a lot in a neonatal ICU. It's used in small children. When it first started to be used frequently, there was really no data to support its use or to know what doses to use. And as I was seeing babies in the NICU, I came across some PK data that was published -- not by the FDA but by some investigators -- that showed, if you were going to use it, you should dose it at least every eight hours or more frequently because the babies metabolize it very quickly. Very few people do that. It was very hard to find that data. I had to dig for it. And, now more recently, there's data published in the medical literature that it really isn't effective. That data's not -- you have to go search for that. It's not on the label. So I think any data that is good data -- we don't want bad data -- that can help us is helpful to have in a PI even if it's not a pediatric indication because there are many situations where drugs are going to be used off label when there's no other good choice. So it's very helpful to have PK data if it's available, safety data if it's available, and efficacy data if it's available.

DR. WADE: Kelly Wade. So maybe just to play devil's advocate though, Dr. Callahan, and for the sake of conversation, when the numbers are so limited and the dropout rate and efficacy and some outliers in their PK levels bring to question the quality of the data or the robustness of the interpretation, how do you put qualifiers in the label to say this is the data that we have but these are limitations? You know, in a peer-reviewed publication, there would be a long description of limitations, so how do you recognize the robustness and quality of the data when you summarize it in a label?

DR. CALLAHAN: Well, I think it needs to have some mechanism where it's been reviewed, and some statistics applied where that's necessary. I'm not saying I know how to do that but --

DR. HAVENS: When a drug goes for a new labeling approval, you get the statistical review. I mean, the OxyContin statistical review that you sent out to us has a boatload of information, and that's available on the FDA website. But I don't know if that would go into what you put into the label for something that wasn't asked to be labeled, right, that we got three PDFs about OxyContin data that allow you all of those indications, the Clin. Pharm. review and the clinical review and the statistical review allow you that broad view. Do those documents exist for this proposed change in the label here that's not going for a new indication?

DR. WADE: Can you clarify the question?

DR. FIELDS: You're asking when the reviews get posted or when the label gets posted?

DR. HAVENS: Opana is not going for a new pediatric indication.

DR. FIELDS: Right.

DR. HAVENS: But you're suggesting that you might modify the label. I like having a modified label because it is a great place to find data that has been evaluated by the

FDA. When there's a new label with a new indication, you get the Clin. Pharm. review and all that stuff and the summary review. Do you get the same level of supporting documentation if the label is changed without a new indication?

DR. FIELDS: Well, the label itself would be posted on Drugs@FDA.

DR. HAVENS: Right.

DR. FIELDS: You're asking whether the reviews are posted. Frankly, I'm not sure.

DR. HAVENS: That's the question.

DR. FIELDS: It's possible they're not. But I don't know for sure. We can try to find out.

DR. LLOYD: It depends on the circumstances.

DR. FIELDS: It does depend on the circumstances. I think for an efficacy supplement, which this would be they may get posted. It's not up to the division. There's people who --

DR. LLOYD: And if they're not posted, I believe there is a process for the public to request that they be posted.

DR. HAVENS: I can't hear you.

DR. LLOYD: This is Josh Lloyd, FDA. If they're not posted, and I'm not a hundred percent sure, but I believe there is a process for the public to request that those reviews be posted.

DR. HAUSMAN: Hi. This is Ethan Hausman from DPMH. Generally, if studies are completed in response to PREA-requirements, the studies are posted in some fashion.

DR. STAFFA: The reviews.

DR. HAUSMAN: The reviews. I'm sorry.

DR. FIELDS: So we're looking at --

DR. PATEL: Drugs@FDA.

DR. FIELDS: -- Drugs@FDA and it looks like there are some --

DR. PATEL: Labels posted but not the review.

DR. FIELDS: No, the labels are posted but not the review, but let me click one more thing.

DR. MEISEL: Even if the reviews are posted, for a front-line clinician finding all that stuff or requesting they get posted, that's not -- I would not call any of that readily available. Let's not fool ourselves into thinking that posting stuff on the website in some obscure place is the same as making the information available to a front-line clinician.

DR. FIELDS: You're exactly right.

DR. WADE: Dr. Kulldorff.

DR. KULLDORFF: Thank you. Martin Kulldorff. The existing label says that in 8.4 pediatric use as the safety and effectiveness of Opana in pediatric patients below the age of 18 years have not been established. I think that that label is still an accurate assessment, and the three studies that we are seeing doesn't really change that. There were 112 or 113 total people, and that's not enough to establish safety. And even worse of those, only 58 received the tablet, and even worse than that, only 20 of those actually continued on the treatment. So, to pretend that we could say anything about the safety of this drug based on these three studies, I think, it doesn't make any sense. And the proposed wording that's listed gives you like a false sense of safety which I think is worse than not having any additional information there. So I think that the current label is accurate, and I don't think there's reason to change it.

DR. WADE: I promise, everyone, I do have a list of people with their flags up, so keep them up if you still have questions. Dr. Jones.

DR. JONES: Thank you. Bridgette Jones. First off, I just wanted to kind of talk

about the -- our goal is -- the fact is that children have pain and children need to have their pain treated. And, ideally, we would like to have rigorous, well-controlled clinical trials to define safety and efficacy, but that's not always feasible. That's not always possible. It's not always ethical to do, for example, blinded studies in kids for pain or any human being really. And so then we have to go with what's the next best alternative, and I think information is always helpful. PREA and BPCA have allowed us to have a lot more information about how we are able to use medications in children. Despite PREA and BPCA, we still have the fact that more than half the drugs that we use on a daily basis in kids are used without information. Dr. Foster talked earlier about in her practice in oncology more than 90 percent of the drugs that she uses are used without information. And so the fact is these drugs are going to be used regardless of whether there's labeling or whether there's information, and so I think that when we have information that may be helpful to prescribers it's important to include that information and provide it in the label.

I do have concerns that or I do think the FDA needs to make sure that when information is included is that it's the complete story. And I feel like some of the information that's been suggested by the sponsor does not tell the complete story of the information that we currently have. So 2 of the 20 some-odd patients had exposures that were much higher. Yes, one maybe was an erroneous PK profile, but that leaves one which is five percent of the population that maybe had a higher exposure. I think that information would be useful to prescribers to have that. Also the fact that among the patients/participants in the study there was a high withdrawal rate due to lack of efficacy. It appears I believe that that information would be helpful for prescribers. I think that sometimes we're making the assumption that if information is placed in the label that means that that's promoting use of that medication, but that may not always be the case; putting the right information in the label may be helpful to prescribers to say, well, maybe I shouldn't use this medication because, again, people are using

it off label and sometimes assuming that it has this similar efficacy and similar safety profiles of adults. So I think including the information is very important but making sure that it's the complete information and that the most pertinent information that prescribers need to make those types of decisions are included.

MS. OSTER: Randi Oster and I'd like to support Dr. Jones and what she has just said. But I'd also like to say is that we have the facts. There's been a tremendous amount of work done. The research is here. We have the statistics. And so, therefore, in the labeling you might say there's dizziness or nausea, but the research that we've read actually give us the numbers behind that. And so, for the labeling, I think we can be specific, and we can say that we did this study and it has a 95 percent plus or minus 20 confidence level. I think that, if we give the facts and take the work that you've done and put it in the label, it will provide the pediatricians the information they need to make an informed decision to use or find alternatives if they think that will work.

DR. WADE: Ms. Robotti.

MS. ROBOTTI: Hi. Suzanne Robotti. I totally support adding information to the labeling that isn't just positive but also shows negative results. We talked about how important it was for studies that have negative results to be published; they should be on the labels too. But I'm going to state -- I'm concerned about the parents. I mean, the parents have the right to know that a drug being given to their child has not been proven safe and effective in children. Don't kill me. I know 90 percent of all the drugs given to them -- but where's the parents' right in here to know the risks that's being taken with their child.

And I'm also going to state that most non-medical people believe an analgesic works. They expect that, if you take a Tylenol, your headache's going to go away, and, if it doesn't, they take a second one or a third or a fourth. This is a concern to me given the nature and relationship of exposure to adverse events and addiction when using opioids. Therefore, I

suggest that not on the label but on the packaging, there'd be a message to people that 58 percent of children using it found it to be noneffective to the point of not continuing to use it, that 66 percent is side effects. Maybe this all comes down to about 25 percent of those who use this product receive the pain relief anticipated, and it should say, if you do not receive pain relief from this product, do not take more. Instead, work with your doctor to seek out alternative pain options that might work better for you. So I think the limitations of the product need to be upfront because it's so important to not use it if it's not working for you.

Also, medication guides, in our briefing material, we were told that we're going to talk about all sorts of ways of alerting people and the medical community about this, but we haven't -- we're really just talking about the label. Medication guides are, as I understand it, written for people to understand. They're not for the medical personnel. They're to be handed to the patient, to the parents, so that they can fully understand. And they're written in consumer language so that they can fully understand the risks, the benefits, the anticipated outcome of it. So let's get a medication guide for this.

DR. FIELDS: Hi. It's Ellen Fields from DAAAP. All opioids come with medication guides.

MS. ROBOTTI: I'm sorry. I actually asked the question a few days ago and got the opposite answer, so I'm so glad to hear that.

DR. FIELDS: There's a one-page medication guide that comes with every opioid -- it's supposed to come with every opioid prescription. It's up to the pharmacy to provide it.

MS. ROBOTTI: Good. I hope it says some of the stuff we've done today.

DR. FIELDS: We're also working on including risk messages on the packaging that's in process. On the packaging, as they say, limited real estate, you can't put long lists of things, so we're having internal discussions and committees working on what should be on opioid packages in terms of risk messaging.

MS. ROBOTTI: Addictive products like cigarettes have limited real estate too.

DR. FIELDS: Right. So we will have some risk messages. We have to select them carefully.

DR. WADE: On the back microphone.

DR. RACOOSIN: Thank you. Can you hear me?

DR. WADE: Yeah.

DR. RACOOSIN: My name is Judy Racoosin, and I'm the deputy director for safety in the Division of Anesthesia, Analgesia, and Addiction Products. I feel like the discussion a few minutes ago raised the issue of how hard it is to access the product labeling, and this circles back with this mention about the medication guide. So I felt that I needed to stand up here and say there is a website called Drugs at -- and it's with the at sign -- FDA. If you go to drugs@FDA, and you put in the drug name that you're interested in, you will get a list of various products, formulations of that drug moiety that you put in there, or if you use the brand name, you'll get the brand name. And there's a vast amount of information that is accessible to you from that page. The original approval letter will be in there. All of the different labeling changes that have occurred over time will be in there. And you can click on the most recent label, and you can access the medication guide from that page. So I just want to make sure we're all on the same page here. This information is very accessible and it's just a matter -- there might even be an app although I can't promise that, but -- okay, I'm getting a nod. So I just want to encourage you all that this information is very accessible, and I hope that you avail yourselves of it in the future.

DR. WADE: Thank you for that. So, being cognizant of time, it's almost 4:40. There are discussion points that we did not quite get to. I think we can spend about five more minutes before there is a call to vote on the final question which may need some clarification. So, in the remainder of the time that we have, I think we've been clear that we think pediatric

information is valuable in the label, that providers are seeking more information and parents are seeking information about medications in the pediatric domain, that we're struggling with the sample size and the quality of the data or the variation in the data that's being submitted.

The final questions 3 and 4 relate to the extrapolation of efficacy in adults to pediatric down to two years of age for opioid analgesics, if there's a specific comment related to that, and the question for which I think we've already spent some time today talking about which was in regard to the two patients with high systemic exposures being eight percent of the pharmacokinetic sample set. So just a couple of minutes, any comments that people want to provide about extrapolation or additional information not already said about the two patient outliers. Dr. Meisel.

DR. MEISEL: Steve Meisel. Thank you. I'll be brief. About the labeling, regardless of what we all believe here, it is an incentive to the manufacturer to have references to pediatric or other populations in the label without having an indication because that way they can have their cake and eat it too. They can semi-promote the use of the drug and not have the liability if something goes south with a patient because, well, it wasn't indicated; that was your choice, doctor. So I think we need to be clear about that, that there's ulterior motive for the vendors in this space to go that way.

The FDA, as valuable as the package insert is, is a regulatory body. It is not an independent comprehensive drug information center and shouldn't be thought of as that. If you want comprehensive drug information about all the studies in pediatrics or some other population or whatever, you can go to Micromedex; you can go to Hippocrates; you can go to all sorts of very comprehensive websites and that should be the go-to source and not rely on the limited real estate that may be in a product insert. So those are elements that I think we need to consider as we consider whether or not to put this new information into the product labeling. And I'll just reiterate the point that I made earlier because I feel very strongly about it; the two

outliers, I don't believe, are outliers in the classic sense that one patient, who had a blood level of ten-fold higher or whatever than the average was, until somebody were to prove to me that there was a lab error, that was real. The patient didn't have a negative response to that because we got lucky or because there's something about the pharmacodynamics of this drug in pediatrics that we don't understand, that didn't cause that sort of harm that we would otherwise expect in adults. But I think it's a signal that blood levels and response to this drug in pediatrics is all over the map unpredictable, and we shouldn't be relying on the pharmacokinetics that we've seen to predict clinical outcomes.

DR. WADE: Terri.

DR. VOEPEL-LEWIS: Thank you. The only thing that I would add in agreement with, any labeling should include all the kids that were excluded and why because we're getting really limited data. And I'm really concerned about the kids that were excluded for adverse events as well as the lack of efficacy because the way that the Opana group has recommended the labeling be doesn't include those children at all.

DR. WADE: Dr. Portman.

DR. PORTMAN: So I want to comment on the extrapolation issues. So the FDA and the company agreed that this would be an extrapolation of efficacy which basically means that the drug was proven to be efficacious in adults. We look at safety which was done granted it's a small population, and so long-term types of follow-up and pharmacovigilance is needed. And we determined the dose through a PK study and what was determined is that it was the dose that was equivalent to the five-milligram dose for adults. What was shown was that these kids, at that starting dose, seemed to have a higher withdrawal rate and that clearly needs to be in the label as well. We don't know that the drug itself won't work at higher levels. And, in fact, remember that this is a single-arm trial. We don't know if there was a placebo group that there wouldn't have been 99 percent withdrawal on the placebo side. So I think all

that has to be taken into consideration and labeling should definitely be included for this drug.

DR. WADE: Dr. Patrick.

DR. PATRICK: Stephen Patrick. I think the question around extrapolation -- it seems like PK data can be reliably obtained with simulation and things like that. It's really a question of data quality in terms of the cohort. Does it really apply? And it seems like -- at least the two that I've been in -- it's the same issues where there's a lot of concerns about both the population -- really, the question is, can we reliably extrapolate at all, and do these data actually help inform us? And it seems like some of this could be due to chance. It could be due to the cohort. There's so much bias that could be in this sample. And, I guess, the question is, is there a way -- because it seems that it's a repeated -- at least in my N of two which also could be chance -- it seems that the same questions come up. So is there a way to sort of standardize in the label PREA of, like, we're able to obtain PK data? We can't look at safety and efficacy. It just seems like we need more data in terms of potential PK, but it doesn't seem like this gives us any information. It just gives us concerns about safety and efficacy.

DR. WADE: For the sake of time, I just want to clarify with my FDA colleagues if they would like to spend the last ten minutes hearing further discussion or if you would like us to move forward with the vote.

DR. FIELDS: It's Ellen Fields. I think we can move forward with the vote.

DR. WADE: So I apologize to those who I did not have time to call upon. But, for the sake of time, we need to wrap up with the final voting question which is shown here on the bottom of the slide. Voting Question Number 2: should pediatric labeling be approved for Opana IR immediate release oxymorphone? And, if so, how should the pediatric information be described in the labeling? I believe this is a yes/no vote to the Question Number 2 posed. And, in the discussion around the table, when you announce your vote, that would be your opportunity to state how you would like the pediatric information to be described in the label

depending on your answer to the question at hand. Are there any questions regarding the specific wording of the question that we need to clarify before we vote?

DR. CZAJA: It's Angela Czaja. I just wanted to clarify. When it says pediatric labeling be approved, does it mean we're approving the specific statements that were put on the slide or what exactly are we approving?

DR. FIELDS: Ellen Fields from DAAAP. No, it doesn't mean those specific sponsor-proposed language, just do you think there should be anything in the label as a result of these studies?

DR. CZAJA: Any of the pediatric data that was described in the studies?

DR. FIELDS: Yeah. Anything that was in the studies that you heard about; do you think it should be included?

DR. WADE: Okay, then, again, if there's no further discussion and given the sake of time, we will now begin the voting process. You'll be using paper ballots. Voting Question Number 2 is printed on blue paper. You will have 60 seconds to vote. After everyone has completed their vote, the members of the Office of Pediatric Therapeutics will collect the ballots. The vote will be displayed on the screen. The DFO will read the vote from the screen into the record, and we will, then, go around the table. And everyone who voted will state their name and vote into the record. If you wish, you can also state the reason why you voted as you did. This will now begin our 60 seconds of voting.

While they're totaling the vote, I just want to give a heads up for tomorrow morning. For the sake of time, we'll be adjourning in this room at 8:30. There's a very busy agenda, and I'm sure everyone's reviewing the briefing documents. But there will be five presentations from the FDA in the morning about the safety events with montelukast, followed by a break, and then an open public hearing which is predicted to take approximately 90 minutes to hear public comment. And then after that time is when we will really open up the

floor for a more robust discussion as we have had today, and this committee is very good at that. So I just wanted to lay the groundwork for tomorrow.

DR. HOLUBKOV: May I ask a logistics question. Have the shuttle times been -
- this is Rich Holubkov -- just for the logistics tomorrow, when will the shuttles --

DR. WADE: The shuttle time tomorrow morning -- that's an excellent question of which I do not know the answer.

MS. BRILL: I believe it's at 7:20.

DR. MEISEL: I was told it's the same for at least with the DSaRM people.

DR. WADE: The same, so 7:20 was the time today --

MS. BRILL: For the PAC.

DR. WADE: - for the PAC --

MS. BRILL: 7:40 for the DSaRM people.

DR. WADE: -- and 7:40 for the DSaRM.

DR. WADE: I would also say there's a 5:00 shuttle back to the hotel which is why we're attentive to the time, or you can find your own transportation, of course. The other announcement is that you do have the option of leaving your folders on the table or taking the folders with you, but if you take your folder with you and you're coming back for the meeting tomorrow, please remember to bring your folder back with you because the folders put out today do contain the information for tomorrow's meeting as well.

We're just waiting for the vote.

MS. BRILL: We're done. Okay. For the record, the results are 8 yes, 16 no, and 1 abstain.

MS. OSTER: So what happens now if we have a majority no? What happens?

DR. WADE: It's simply the information from the Pediatric Advisory Committee that is available to the FDA. So we now have to go around the room as we did before, please

state your name and your vote and if you wish any further comment. We'll start on the left side of the room with Dr. Sleeper.

DR. SLEEPER: Lynn Sleeper and I voted no.

DR. HOLUBKOV: Rich Holubkov. I voted no. I agree with all the good points that were made about the utility of labeling. But the particular data set here is very small, very shaky. We've got those two possible --

DR. KULLDORFF: Your microphone went off.

DR. HOLUBKOV: Sorry. I don't think it's going to be on anymore.

DR. KULLDORFF: That's all you have to say on the topic.

DR. HOLUBKOV: Mr. Speaker, I've been cut off. But I believe that the particular data set here was rather small. That signal 2 out of 24, which we're not sure we believe that can translate into -- we can't rule out that -- if that exists, we cannot rule out that in a quarter of the population using 95 percent confidence intervals, yet we're not sure we believe that signal. So, looking at the data provided, it would be very difficult to put that on the label. That would be utilitous (phonetic) in my judgment.

DR. KULLDORFF: Martin Kulldorff. I voted no. I think the current label is an accurate assessment of the situation and any discussion about the pediatric safety would just give a false safe sense of security for the drug.

DR. HABEL: Hi. My name is Lori Habel. I voted yes. There's very little data, so that some data's better than nothing as long as it's appropriately described. The limitations are appropriately described. For example, with safety signals, I think you could say that we could not identify signals that occur in less than one in a hundred patients or something, I mean, some way to put in the appropriate caveats. Maybe that's not possible, but that would be my suggestion.

DR. CZAJA: Angela Czaja. I voted no, similar concerns about being able to

interpret the data easily on the label although I would like to see if it's able to be available in another format so that somebody who wanted to dig a little bit further and see what data is out there could find it and spend the time really looking at the data carefully.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes with a but. I wanted to provide some information to the fact that some studies had been done, but with a caveat that it's one thing to inform practice and another thing is to put in the label. And maybe putting too much in the label could give the false impression of having the evidence of safety or efficacy. And I will be surprised maybe if the following day, we would see an announcement that this is the first drug approved for kids under 18, and that's probably not what we want. So I think, whatever we put, we have to be careful with potential implications of the label to the question that we had before in terms of use for good management of pain, but also for potential overuse and abuse.

And then the second point was what to add. And I think that's where it would be important if you decide to include, with PK studies for utilization, but suggested a dose that doesn't seem to have effectiveness, like at least 50 percent of kids who didn't get a benefit. And we don't know if placebo would have actually had the same benefit just from waiting. And we, of course, don't know if NSAIDS will have better efficacy. What we do know I think is only adverse effects that were already known and the potential for abuse and overuse. So I think, if anything goes, it has to be carefully drafted.

DR. ORTIZ-AGUAYO: Roberto Ortiz-Aguayo. I voted yes with the qualifiers that there should be some specifiers as to the data, the N, as well as the efficacy and dropout rates. I also believe that because we do know that the off-label prescribing particular in chronic pain conditions is more likely to happen than not. Some data is better than no data.

DR. MCGOUGH: Jim McGough. I voted a rare no. I'm generally not comfortable with putting data from non-indicated conditions into the label. It's just a slippery

slope, and I'm just not convinced that it's worthwhile. And secondly, this data set is noninformative. I have no idea what to do looking at this, and I read, well, it didn't really work, and the doses were weird, so do I double the dose? Do I triple the dose? I have no idea as a practitioner. This doesn't guide me at all in terms of using this drug or managing the pain, so if we're going to do it off label, it's on me. I think having this in the label is just confusing.

DR. PARRONE: I voted no, and I agree with everything that's been said.

Jeanmarie Perrone.

DR. MEISEL: Steve Meisel. I voted no for reasons previously stated.

DR. VOEPEL-LEWIS: Terri Voepel-Lewis. I voted no for the same reasons.

DR. LESAR: Tim Lesar. I voted no as well for similar reasons.

DR. HOEHN: Sarah Hoehn. I voted no primarily because I didn't think we could negate those two children with the really high levels. And I was afraid that, if it was approved, then we'd start seeing potentially fatal outcomes from it, and I didn't think we should take that chance.

DR. TURER: Christi Turer. I voted no. I think we need dose-escalation data to really understand the benefits and risks. I think if you look at that table and the PK data indicate that your C_{max} goes up with dose, you might think, well, if I just increase the dose, I'll get better efficacy, but, in truth, the efficacy was no better. So we don't have sufficient data that if you increase the dose, you get safe, effective drug without the risks.

DR. CALLAHAN: David Callahan. I voted yes. I'd like to see the PK data, and I'd like some clarification from the FDA about a comment from earlier discussion. It's my understanding that, if you put pediatric information in the label, that does not give permission to the sponsor to market or promote the drug for pediatric use. My understanding is you have to have a pediatric indication for them to do that. Is that correct?

DR. FIELDS: They can market it for use with an indication. However, they can

-- anything that's in the package insert in the label can be conveyed in some way. It's not a secret. So they can't say it's indicated, but they can say we got PK data, and here it is in the label.

DR. SAYEJ: Wael Sayej. I voted yes reluctantly, but I think that the more data that we have, the better obviously, and I think a robust study in pediatrics is worthwhile. However, just as Dr. Callahan just mentioned having the data in the label does not necessarily mean that it is indicated for use in pediatrics. And as long as there's a clear language in the label saying that this is not approved in pediatrics, I don't see what the issue is with adding more information about pediatric use or pediatric dosing. Well, actually, forget pediatric dosing. I don't think it should be in there at all, but we just have to say that it's been tested in pediatrics, and the data is inconclusive, for example, with no definite dosing required recommendations or PK levels or anything like that. Until we have more robust data and more information, then we cannot -- that can always be updated and revised.

DR. HAVENS: Peter Havens. I voted yes understanding that the FDA might be able to present the data in a way that it would seem really negative to anybody reading it based on the data we saw.

DR. ANNE: Premchand Anne. I voted no.

DR. PATRICK: Stephen Patrick. No for reasons already stated.

DR. FLICK: Randall Flick. I voted no, although I think the arguments about the placement of information in the package insert, the label, is a good one. I think there's an implicit endorsement of the drug for use in pediatrics in that label change. I suspect that's why the sponsor asks for it. They expect that they'll sell more drug because it's there. And I don't think any one of us think the data that was presented would imply or ensure safety.

DR. GRIFFIN: I'm Marie Griffin. I voted no. I think it would be of use for practitioners to have this information, but I don't think the package insert is the right place. And

it would be great to have somebody do a commentary on this. And, with all the information that we do have on what actually happened in these trials, I think it would be good for practitioners to know this.

DR. WILFOND: This is Ben Wilfond. I voted yes, although I was persuaded by the no voters who made the comment about off labels means no label, and that probably might have changed my vote. But, more importantly, I also voted yes because of this naïve belief that somebody else mentioned that, if this was presented with the appropriate interpretation, this ought to be a very strong message to not use this in children. And the question that maybe that is unclear to me is to what extent would that language be so interpretive. I was very impressed by the last two slides of the presenter in the morning. That really kind of made me wake up, and I would worry that that needs to be written very clearly to the practitioners. But more importantly, in terms of giving out medication guides, it would be important for a parent who received this medication to be able to read that very carefully and, without any nuance, get that point as well. And so maybe I'm not quite sure where that leaves me after saying all that.

MS. OSTER: Randi Oster. I voted no for the reasons that have been stated, but I'd also like to share that I know what it's like to have a child screaming in pain. On a scale of one to ten, my child yelled out 12 with the F word. And, if he had been given a drug that I would have assumed was FDA approved, I would have assumed that the work or the data behind it was there, and, therefore, with that context, I'm happy to see that we will move forward to make sure we get the information we need so that, when children are in pain, that the safety is there.

MS. ROBOTTI: Hi. Suzanne Robotti. I abstained which does not mean I didn't vote. It meant that I was not comfortable voting yes or no. There are times when one should put information on the label for a nonindicated group, but I'm not convinced that this is one of those times. The data from these studies was not helpful to prescribers. And, if we continue to

accept data from studies we find to be unhelpful or less than robust, we will continue to get those studies. We have to find a different way to get the data set higher with more clear results.

On the other hand, there was an indication about efficacy in this study. It wasn't positive; it wasn't helpful, but it might warn doctors not to use this or to be very careful in using this product because doctors are using it in pediatric areas. So I would encourage, if the label information does have pediatric information on it, it should have a specific reminder on it to doctors that studies to date have not proven this drug to be safe or effective for children.

MS. CELENTO: Amy Celento. I voted yes. I'm very much in Dr. Wilfond's camp. Thank you.

DR. WADE: Thank you, everyone, for this robust discussion today and staying a few minutes late at the end. This meeting is now adjourned.

[MEETING ADJOURNED]