UNITED STATES FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Bethesda, Maryland

Tuesday, April 12, 2016

PARTICIPANTS:

Welcome and Introductory Remarks:

MARK HUDAK, MD
Chair of Pediatric Advisory Committee (PAC)
Chief, Division of Neonatology
University of Florida, College of Medicine
Assistant Medical Director
National Intensive Care Unit
Wolfson Children's Hospital
Jacksonville, Florida

Introduction of New Designated Federal Official and Award Presentation:

ROBERT "SKIP" NELSON, MD, PhD
Deputy Director, Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration

Opening Statement:

MARIEANN R. BRILL, MBA, RAC, MT (ASCP)
Designed Federal Official, PAC
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration
Silver Spring, Maryland

AAP Presentation:

CHRIS FEUDTNER, MD, PhD, MPH, FAAP
Chair of the American Academy of Pediatrics
Section on Hospice and Palliative Medicine

Analgesic Development for Pediatric Patients:

SHARON HERTZ, MD
Director, Division of Anesthesia, Analgesia and Addiction Products
Center for Drug Evaluation and Research

PARTICIPANTS (CONT'D):

Open Public Hearing:

MARK HUDAK, MD
Chair of Pediatric Advisory Committee (PAC)
Chief, Division of Neonatology
University of Florida, College of Medicine
Assistant Medical Director
National Intensive Care Unit
Wolfson Children's Hospital
Jacksonville, Florida

Abbreviated Presentations:

FluLavel Quadrivalent, FluLaval, and Fluzone Quadrivalent (Influenza Vaccines):

LCDR KENNETH QUINTO, MD, MPH
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration

SKYLA (Levonorgestrel-Releasing Intrauterine System) and Xeloda (capecitabine):

JUDITH U. COPE, MD, MPH
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration

MYCAMINE (micafungia sodium):

LCDR ERICA RADDEN, MD
Division of Pediatric & Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

PARTICIPANTS (CONT'D):

Noxafil (posaconazole):

AMY TAYLOR, MD
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration

Risk-Based Assessment Proposal:

LCDR KENNETH QUINTO, MD, MPH
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration

Precedex (dexmedetomidine hydrochloride) and Aciphex Sprinkle (rabeprazole sodium):

AMY TAYLOR, MD
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration

Vyvanse Capsules (lisdexanfetamine dimesylate) and SYMBYAX (fluoxetine hydrochloride and olanzapine):

MONA KHURANA, MD
Division of Pediatric & Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Seroquel (quetiapine fumarate) & Seroquel XR (quetiapine fumarate extended-release) and Sabril (vigabatrin):

DIANA SNYDER, MD
Division of Pediatric & Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

PARTICIPANTS (CONT'D):

Center for Devices and Radiological Health; Annual Update of Post-Market HDE Reviews:

Medtronic Activa Dystonia Therapy:

COURTNEY MILLIN, PhD
Product Evaluation Branch III
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Food and Drug Administration

Liposorber LA-15 System:

DOUGLAS SILVERSTEIN, MD
Medical Officer
Renal Devices Branch
Division of Reproductive Gastro-Renal and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

Initial Post-Market HDE Review:

Impedia RP System:

JOHN LASCHINGER, MD
Medical Officer
Structural Heart Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

PARTICIPANTS (CONT'D):

Wrap-Up and Adjournment:

MARK HUDAK, MD
Chair of Pediatric Advisory Committee (PAC)
Chief, Division of Neonatology
University of Florida, College of Medicine
Assistant Medical Director
National Intensive Care Unit
Wolfson Children's Hospital
Jacksonville, Florida

Other Participants:

SUSAN BAKER, MD, PhD
Co-Director, Digestive Diseases Nutrition Center
Children's Hospital of Buffalo
Professor of Pediatrics
The State University of New York

MARY CATALETTO, MD, FAAP
Attending Physician
Winthrop University Hospital
Mineola, New York
Professor of Clinical Pediatrics
SUNY Stony Brook
Stony Brook, New York

AMY CELENTO, BS
Committee Member
Pediatric Advisory Committee
Food and Drug Administration
Nutley, New Jersey

AVITAL CNAAN, PhD
Director, Multi-Center Studies Section
Center for Clinical and Community Research
Children's Research Institute
Children's National Medical Center
Washington, D.C.

PARTICIPANTS (CONT'D):

ROBERT DRACKER, MD, MHA, MBA, CPI
Medical Director, Summerwood Pediatrics
Founder, Infusacare Medical Services, P.C.
Liverpool, New York
Chief of Service, Department of Pediatrics
Community General Hospital
Syracuse, New York

RONALD PORTMAN, MD
Executive Director, Pediatric Therapeutic Area
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

JONATHAN MINK, MD, PhD
Chief, Child Neurology
Golisano Children's Hospital
Professor, Child Neurology
Frederick A. Horner, MD, Endowed Professorship
in Pediatric Neurology
University of Rochester Medical
School of Medicine and Dentistry
Rochester, New York

MICHAEL WHITE, MD, PhD, FACC, FAAP
Pediatric Cardiologist
Ochsner Health System
New Orleans, Louisiana

Consultants:

JEFFREY CAMPBELL, MD, MS
Director, Nemours Neuroscience Center
Nemours/Alfred I. DuPont Hospital for Children
Wilmington, Delaware
Assistant Professor, Neurosurgery
Thomas Jefferson University
Philadelphia, Pennsylvania

PARTICIPANTS (CONT'D):

MELODY CUNNINGHAM, MD
Medical Director
Palliative Medicine Service
Le Bonheur Children's Hospital
Associate Professor of Pediatrics
University of Tennessee, Medical School
Memphis, Tennessee

JONATHAN DAVIS, MD
Chief of Newborn Medicine
Floating Hospital for Children
Tufts Medical Center
Professor of Pediatrics
Tufts University School of Medicine
Boston, Massachusetts

PETER HAVENS, MD, MS
Director, Pediatric HIV Care Program
Children's Hospital of Wisconsin
Professor, Pediatrics
Medical College of Wisconsin
Milwaukee, Wisconsin

SARAH HOEHN, MD, MBe, FAAP
Associate Professor, Pediatrics
University of Kansas School of Medicine
Attending, Pediatric Intensive Care Unit
University of Kansas Medical Center
Kansas City, Kansas

FREDERICK KASKEL, PhD, MD
Professor, Department of Pediatrics
Director of Child Health, Einstein CTSA
Montefiore Medical Center
Albert Einstein College of Medicine
Bronx, New York

PARTICIPANTS (CONT'D):

MARC MOON, MD
John M. Shoenberg Chair in Cardiovascular Disease
Chief, Cardiac Surgery
Director, Center for Diseases of the Thoracic Aorta
Program Director, Thoracic Surgery Residency
Washington University School of Medicine
Saint Louis, Missouri

ALEXANDER RAKOWSKY, MD
Assistant Professor, Department of Pediatrics
Division of Ambulatory Pediatrics
Attending, Resident Teaching Clinics
Program Director, Pediatric Residency Program
Nationwide Children's Hospital
Columbus, Ohio

KENNETH TOWBIN, MD
Chief, Clinical Child and Adolescent Psychiatry
National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

CHRISTY TURER, MD, MHS, FAAP, FTOS
Assistant Professor, Pediatrics, Clinical Sciences, and Medicine
Director, General Academic Pediatrics Fellowship
UT Southwestern and Children's Medical Center
Dallas, Texas

LESLIE WALKER-HARDING, MD
Vice Chair, Department of Pediatrics
University of Washington School of Medicine
Director, University of Washington Leadership Education in Adolescent Health
Affiliate Faculty, Maternal and Child Health
University of Washington School of Public Health
Seattle, Washington

P R O C E E D I N G S

(8:05 a.m.)

DR. HUDAK: It's a little bit after 8:00 o'clock. Welcome to the FDA Pediatric Advisory Committee Meeting today. We have a rather full agenda, including a working lunch. And if we are on time we'll get out by 5:30.

So, we've got multiple items on the agenda today including an initial sort of presentation set up for a larger meeting on opioids, and we'll have some guest speakers for that. But I think, why don't we go around the room and I see new faces here, so starting over at this end of the table, if you could sort of introduce yourself, and say what you do and where you are from?

DR. PORTMAN: Okay. I'm Ron Portman, I'm a Pediatric Nephrologist, and I work as the Director of Pediatric Therapeutic Area, at Novartis Pharmaceuticals.

DR. WALKER-HARDING: Leslie Walker-Harding, and I'm Adolescent Medicine, Chief

in the Division of Adolescent Medicine, and Vice Chair PDS, at the University of Washington.

DR. TURER: Christy Turer, I'm am a Medicine Pediatric Physician. I do research in obesity medicine, and I'm the Director of the Academic Fellowship at UT Southwestern Medical Center, for Pediatrics.

DR. BAKER: I'm Susan Baker, I'm Professor of Pediatrics, Pediatric Gastroenterologist at the University of Buffalo.

DR. KASKEL: Rick Kaskel, also Pediatric Nephrologist at Albert Einstein in the Bronx, Vice Chair and Head of Child Life Research.

DR. MINK: I'm John Mink. I'm a Pediatric Neurologist and Chief of the Division of the University of Rochester, and this is my swan song.

DR. CUNNINGHAM: I'm Melody Cunningham, Pediatric Hematology, Oncology, and Pediatric Palliative Care, and I'm the Medical Director of the Program at Le Bonheur Children's Hospital in Memphis.

DR. HOEHN: Sarah Hoehn, Pediatric Critical Care, University of Kansas, Associate Professor, Pediatric Hospice and Palliative Care, and Pediatric Ethics.

DR. CATALETTO: Mary Cataletto, I'm a Pediatric Pulmonologist, and Clinical Professor of Pediatrics at SUNY Stony Brook.

DR. CAMPBELL: I'm Jeff Campbell. I'm Pediatric Neurosurgeon and Director of the Neuroscience Center at Nemours in Wilmington, Delaware.

DR. WHITE: Michael White. I'm a Pediatric Cardiologist with the Ochsner Health System, and I Chair one of our IRBs; and Associate Professor at the Ochsner University of Queensland Clinical Medical School.

MS. CELENTO: Amy Celento, a Patient Representative.

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

DR. RAKOWSKY: Alex Rakowsky, one of the Program Directors in Nationwide Children's Hospital, and proud Alumni of the Committee, like four years ago. So, I guess I'm back.

MS. BRILL: I'm Marieann Brill. I'm the Designated Federal Officer. I'm with the Office of Pediatric Therapeutics.

DR. HUDAK: And the missing seat is Dr. Ken Towbin is coming but he's running a little late. And I'm Mark Hudak, I'm Chair of Pediatrics, and Neonatologist, University of Florida, College of Medicine, Jacksonville.

DR. DAVIS: I'm Jon Davis, Neonatologist from Tufts University in Boston, and I Chair the Neonatal Advisory Committee which is a Sub-Committee to the Pediatric Advisory Committee here at FDA.

DR. MOON: I'm Marc Moon, I'm a Cardiac Surgeon at Washington University in St. Louis.

DR. DRACKER: I'm Bob Dracker, Pediatrics, Hematology and Transfusion Medicine, at Syracuse, New York.

DR. CNAAN: Avital Cnaan, I'm Professor of Biostatistics, Epidemiology and Pediatrics at GW, and Chief of Biostatistics at Children's National.

DR. COPE: Judy Cope, I Head up the Safety Team for the Office of Pediatric Therapeutics.

DR. NELSON: Skip Nelson, I'm Deputy Director of the Office of Pediatrics and Therapeutics.

DR. HAUSMAN: Ethan Hausman, Division of Pediatric, Maternal Health, my background is Pediatrics and Pathology.

DR. ALEXANDER: John Alexander, I'm Acting Deputy Director in the Division of Pediatric and Maternal Health.

DR. HUDAK: Okay. Thank you very much. Just a housekeeping order here; all of the participants of the meeting around the table have a lunch order form. I've been told that if you can fill that out and get that to the relevant people by 10:00 o'clock you will be able to have a

box lunch.

So at this point I will turn it over to Dr. Nelson.

DR. NELSON: Thanks, Mark. And just a quick comment about the lunch, as you can see our agenda is pretty full. We make up a little time in the open public hearing but given what we have to cover today, we figured we'd have a working lunch, and to have a working lunch, it needs to be in open session, so that's just the way it works.

A couple of things, first of all, I'd like to welcome Marieann as the new designated Federal Official. Those that had been on the Committee, remember Walt, maybe you don't, but Marieann is the new Walt. I don't know if you want to say something about your background Marieann?

MS. BRILL: I am Marieann Brill, I had been with the FDA for so many years and then I left to go Fort Detrick, where I was a Senior Clinical -- a Senior Reviewer, I'm sorry, and then from there I came back to the FDA, joined CTP for

about two-and-a-half years, where I was a Branch Chief for, and was responsible for the substantial equivalence programs, and I'm here now in OPT. I'm so glad to be here.

DR. NELSON: And for those not entirely familiar with the FDA acronym, CTP is the Center for Tobacco Products. So one of the, I guess, the most recent center addition to the FDA's portfolio. Then the other item, and to just save time on the ups and downs, there are three people around the table, and one person who is not here, who should have in front of you plaques, commemorating your service on the Pediatric Advisory Committee. Phil La Russa who is not here will be stepping off. He has been a member of the Committee for four years.

Amy, should have -- I don't know if you want to open it up, and you all can just show it for the -- so that everybody can go ooh, and ah, and realize that at the end of their time here, you do in fact get a plaque. Amy has been on the Committee for two tours of duty, and has been a

viable member of the Committee, as our Patient Family Representative for basically since I was 7 with a brief hiatus. So that will be a loss.

And Susan Baker has been on the Committee for four years and, you know, I think you -- as long as you fill out your SGE paperwork we'll keep you coming back, as Alex mentioned. But four years is the term, and of course Jonathan make mention that he's stepping off, and he's got his plaque as well, very nice and suitable to hang, and to remember us by.

So, we certainly appreciate your service, and as I said, as products come back and we need expertise in certain things, as long as you are willing to complete your SGE paperwork, which I realize is a big task, you can continue to be a part of our family around the table, but we certainly appreciate your services, Members of the Committee, and then look forward to whatever interactions we might have going forward when we need your expertise. So, thank you for your service.

So, I think, back to you, Marieann.

MS. BRILL: Thank you, and good morning, everyone. The following announcement is made to address the issues of conflict of interest with regards to today's discussion of reports by the Agency, as mandated by the Best Pharmaceuticals for Children Act, and Pediatric Research Equity Act. Based on a submitted agenda for today's meeting, and all financial interest reported by the Committee participants, it has been determined that those individual who will be participating in each topic do not have a conflict of interest for the following products.

FluLaval Quadrivalent, FluLaval Trivalent, Fluzone Quadrivalent, Aciphex Sprinkle, Mycamine, Noxafil, Precedex, Sabril, Seroquel and Seroquel XR, Skyla, Symbyax, Vyvanse, Xeloda, Impella, Liposorber and Activa.

In general, the Committee participants are aware of the need to exclude themselves from involvement in the discussion of topics if their interests would be affected and exclusion would be

noted for the record. In order to provide the scientific and medical perspectives required to adequately address the products covered in today's meeting, the following individuals were invited to participate as expert consultants and are considered temporary voting members on the Committee.

Dr. Towbin, Dr. Hoehen, Dr. Cunningham, Dr. Walker-Harding, Dr. Marc Moon, Dr. Rakowsky, Dr Kaskel, Dr. Campbell, Dr. Havens, Dr. Turer and Dr. Davis. Ms. Celento is participating as a patient representative which is a voting position. And Dr. Ron Portman is participating as the industry rep which is a non-voting position.

I would like to note that Dr. Portman is not a special government employee. He has the opportunity to sit at the table during discussion of all the products, but he's not able to convey information or opinions related to his particular firm. If a product comes before the Committee that involves his particular firm, then Dr. Portman has the option to step away from the

table.

Therefore, based on our analysis of all the reported interests we received prior to this meeting, we have two recusals. Dr. Mink will be recused from the discussion of Activa, and Dr. Moon will also be recused from the discussion of Activa.

At the time the product comes up for discussions, these individuals will simply step away from the table and just sit in the audience, until the portion of the meeting has finished. With respect to all other participants, we ask, in the interest of fairness, that they state any current or previous financial involvement with any firm whose product they may wish to comment on.

In addition, I'd like to remind the audience that the final version of the materials that will be presented at today's meeting, will be posted on the Pediatric Advisory Committee website. So any copies of slides that you have that appear different from the ones on the screen, will be updated and provided on the website.

As a reminder to the Committee and those around the table, this meeting is being transcribed, and as such, when you are acknowledged to make a statement or have a question if you would, please, press the button on your microphone, and state your name prior to beginning your statement. I'd like to remind the members of the Committee as well, to please avoid any sidebar conversations either at the table or outside of the room during the break, as any kind of information that needs to be discussed on a particular product must be discussed at the table during the session of the meeting. And finally, if you could, please, silence your cell phones to minimize interruption during the meeting.

And at this time I would like turn the attention over to Dr. Hudak.

DR. HUDAK: Okay. Very good. We are already running ahead of time. That's a good trend. So, the next session is a one-hour or so session with some information presented to the Committee about opioids and this is meant to

prepare us for a larger, more robust session in September.

A couple points of procedure here. We have two speakers and at the conclusion of their presentations, the Committee can ask questions to the speakers, but because all of the members of Committee have not yet been screened for any conflict of interest surrounding opioid medications, the questions need to be purely the questions for information only, and not questions expressing an opinion or facts, or whatever that might confuse the situation. So, as I said, this is a preliminary discussion prior to a wider discussion in September.

So our first speaker is representing the AAP I believe, Dr. Chris Feudtner, and his background is that he's a Pediatrician, Epidemiologist, Historian and Ethicist. He currently works at the Children's Hospital of Philadelphia, at the University of Pennsylvania. His focus is on improving the lives of children with complex chronic conditions, and working with

your families as well.

He has participated widely in research, and he has developed clinical programs while taking care of pediatric patients including the focus, I think, on palliative care where, of course, these drugs are a main stay of treatment for some children. He also does clinical ethics consultations, and he points out that his family life is very important, his wife is also a physician, they have three children, and I guess, importantly, two dogs. Thank you.

DR. FEUDTNER: I'm Chris Feudtner, and I want to thank you for having me here today. As a pediatrician who takes care of children with complex chronic conditions, and as mentioned, when needed providing palliative for those children and helping their families as best I can. I have a background doing that, as well as doing pediatric research and ethics consultation. And today, this morning I'm here as a Member of the AAP, representing AAP specifically in my role as the Chair of the section of Hospice of Palliative

Medicine.

I'm here to advocate for two groups of vulnerable children, infants, adolescents, young adults. The first group is at risk for misuse of opioids, taking opioids in a prohibited and harmful manner, and the second group that I'm here to advocate for, are children who are enduring inadequately relieved severe pain. And the task that I see before myself and before us is to figure out ways to be able to serve both of these groups with clear-sighted balanced forthright policy to the challenges that they both face.

The first group ranges in age from infants born to mothers who took opioids during pregnancy to teenagers taking opioids out of family medicine cabinets. The illicit use and addiction that ensures particularly for the older adolescents and young adults is one of, unfortunately, the leading causes of death in that age range. At the other group, a variety of medical conditions can cause pain so severe that the pain is refractory to lesser interventions.

Conditions like cancer sickle cell anemia, pain crises, deforming musculoskeletal conditions, and as members of this group would know from their own clinical practice if you are a clinician, many other rare conditions that can cause states of substantial pain, that is not just acute but chronic.

The goal that we have then is to find ways to balance the needs that both of these groups have to neglect neither group to be able to focus and meet the needs of both. The pieces of that policy puzzle of the solution that is both policy, clinical, scientific, is many fold and I put this slide up here, not to go through it in detail, but to point out the fact that the main topic that I will talk about in a few minutes, i.e. labeling, is but one piece of this much larger puzzle.

And as such, has to be viewed as what labeling can do and what other pieces of the puzzle are going to be required to have an effective response; ranging all the way from the

science, drug discovery, clinical practice, curtailing the availability of illicit sources and coming up with better treatment options for people who have lapsed into misuse.

So, I'm briefly going to talk about that first goal of stopping opioid misuse, not that that is the purview of this Committee but just to put it out there, because it's part of what we need to grapple with. Substance abuse we know often starts in adolescents, adolescents misusing opioids rarely get them as a prescribed medicine from a doctor. Instead, more often it's from the family medicine cabinet or from an illicit street supply.

There is concern, the degree to which we are unclear of at this point, that even appropriate opioid use to treat pain may slightly increase the risk of later opioid misuse.

The AAP has been very active on a couple of fronts to try to address and meet the challenges that this epidemic of opioid misuse. The AAP Committee on Substance Abuse, Substance

Use and Prevention is work to promote the use of a variety of interventions. Screening, brief interventions, and referral for treatment for adolescents particularly in the primary care setting, the development of clinical practice guidelines specifically, again, for adolescents. As somebody said to me, having an adolescent go to an intervention with much older people in their 40s, 50s, just doesn't really work for that adolescent most of the time.

The AAP has also strongly supported the passage this past year of the Protecting our Infants Act, which as you may know has advanced the Federal Government's activity to improve the treatment and identification of babies, and neonatal abstinence syndrome, and equally important to take care of the pregnant women who are addicted to opioids.

We also need, again, not your purview, but just to put it out there, a range of other activities and solutions. Ways to take care of pain that does not require opioids management, a

variety of ways to disseminate proven techniques and, importantly, for those techniques in clinical practice.

We need better opioid return practice policies to empty family medicine cabinets. We need to reduce the total amount that is prescribed in the given prescription, meaning for an acute pain episode, to somebody who really need a 14 or 28-day supply, could that be reduced so there is just medicine dispensed at the time of that acute use, better educational training about preventing drug misuse and access to appropriate, as I already mentioned, age-appropriate addiction treatment.

Let me turn to the group that I spend quite a bit of time thinking about and caring for, those who have severe pain. As mentioned, despite tremendous advances in pediatric care each year just about a little bit under 50,000 infants, children and adolescents die, and about a third of these do so from progressive conditions that often cause substantial pain. And there are many other

children who don't have progressive ultimately fatal conditions that also experience severe refractory, if not treated appropriately, refractory pain.

We do need to develop, again, non-pharmacologic techniques and figure out ways to reimburse them. The more we learn about adjunctive techniques they have a clear role to play, and are largely under utilized for want of the ability to provide that in a variety of setting because of timely reimbursement. We need to have regional and non-systemic interventions that target the area of pain, not necessarily treating the entire body.

The development and testing and ultimately labeling of non-opioid adjunctive medications that help to ease pain either in concurrent use with opioids, or completely independent of opioids. We need better data regarding what are safe opioid prescribing practices to prevent harm and prevent misuse; and then as I've mentioned, because it is a major

stumbling block, reimbursement for the time and effort that it takes to do all of that work.

Inevitably though, even if we come up with all of the other ways to try to limit the need for the use of opioids there will be cases of children with severe refractory pain, who will require short and long-term, long-acting opioids as part of the most effective comprehensive pain management plan. People and, like you said the bodies, that are focusing on efforts to curtail opioids misuse by restricting the prescribing of pediatric patients, more so than adult patients, may be misunderstanding where the illicit drug supply is coming from.

And inadvertently, and largely because, again, the need to keep our eye on both of these goals, putting children who are in pain and at risk for substantial refractory pain, putting them at risk for ongoing pain. I've heard many stories of the concerns at least about the rising needs to actually be able to prescribe opioids for children as on the one hand, we see why that is being

motivated, on the other hand it creates barriers to the appropriate treatment of pain to these children who have chronic conditions that require ongoing opioid medication.

Turning to pediatric drug studies and labeling, as we think about where labeling fits in the flow from science to clinical practice, it is worth realizing that "unlabel" practice, there may be a broader range of practice in terms of having medications that are being used, not only whether they were being used yes or no, but the amount that is being prescribed, the dosage, et cetera.

And one of the goals of labeling is to try to limit that variation and make practice safer and more effective. As such, labeling both points to a direction where the use can be an evidence-based way, shown to be appropriate and effective, and can also, although it doesn't need to do this, it can at times, also point out where use is probably not going to be appropriate, in terms of contra-indications and other sort of ways that the appropriateness of use can be indicated.

If you look, for example, at the label that was actually, the labeling that was offered for Oxycontin, it provides on the one hand, labeling for the indication for pediatric patients 11 years of age and older, but at the same time it places, in a variety of interesting ways, some real high bar benchmarks, in terms of when this medication should be used. And I think that this is an important piece to be emphasized.

It's specified that the patient already had to be opioid tolerant, so this is not a labeling that would be potentially construed as permissive of use of this medication for a population that's not already been on a substantial amount of opioids. As the labeling says, who are already receiving and tolerating a minimum daily opioid dose of at least 20 milligrams of Oxycodone orally or its equivalent.

The point here would simply be, and this is not just saying what appropriate use is, but it's raising the bar and saying this is what each should be used for, and if you are not already at

that state, it should not likely be used; although I'll come back to that, the caveats of that in a minute.

Children differ from adults in ways that this Committee knows all too well, that the drugs can have an effective developing bodies, the rates at which the drugs are absorbed, distributed, metabolized, eliminated, the degree to which the drug is in fact effective, and the side effects, in general, safety profile. So we need to have pediatric drugs doses and labeling.

Congress has recognized the importance of these facts by advancing pediatric health and wellbeing through legislative action, including the Best Pharmaceutical Act, the Children's Act, and Pediatric Research Equity Act. And today, because of those efforts over 615 label changes have been made under that legislation to add new pediatric information, and thereby improve the way that children are treated.

At the same time, we know that off-label use, because so few drugs, relatively speaking,

have pediatric labeling, continues to be a necessary part of pediatric practice, and I want to emphasize that. That off-label use is a necessary part of pediatric practice.

So, the labeling decisions are to help guide pediatric practice, and if they are there can be very, very informative and can provide as I said, both indications for appropriate use, and potentially some constraints, but given the current state of affairs, off-label use as the AAP has tried to argue, and many others have, is an issue of understanding that most drugs don't have pediatric labeling and that the tailoring of treatment for a particular child is an individual decision that has to be guided by the knowledge of the clinician, discussions with the family, to figure out what's the best way to care for that particular patient.

In many ways what I've just said is reiterated here that upwards of 50 percent of the drugs used in pediatric practice don't have labeling, and this is due to the ongoing --

although we've made some strides in this direction, ongoing dearth of research knowledge about drugs in pediatric patients and failing to label a drug does not shut down the use of the drug, in fact, because of this state of affairs, the absence of labeling is not necessarily going to impact the way that the drug gets used if it's a necessary drug to treat the child effectively.

Pediatric drug research also protects children. Studies exposed tens to hundreds of children to carefully- monitored risk in order to protect thousands to tens of thousands of children from unknown, and largely unmonitored risks. And this is why we pursue pediatric research for the ability to improve the overall health of the population. And then extrapolating the dosing effect, efficacy and safety from adult studies to infants and children, is like throwing darts in the breeze.

We don't know exactly where the bias is going to come from, will it be overdosed, underdosed, the direction of the breeze is unknown

to us. It's the opposite of where we are trying to take medicine. It's the opposite of precision medicine. And it's unpredictably inaccurate. We know the children when these extrapolations are made, or are going to wind up getting hurt because we will either overdose or under-dose the medication. And that pediatric drug labeling based on extrapolated efficacy, it can be done somewhat appropriately, but it's much better to have data to be able to base those decisions on.

The framework for labeling pediatric medications, needs to be prioritized, conditions that are common, i.e. Affecting large numbers of children, or are particularly serious, ought to be priority conditions in terms of an indication for moving a drug up in terms of trying to figure out ways to provide effective labeling. The medications that are being used without labeling in ways that maybe less effective and less safe, so it could also be a perusal of the ways that medications are being used that would indicate the need for the introduction of labeling, again,

provided that there's adequate evidence to build the labeling on.

The framework for labeling pediatric medication should be based on rigorous studies, efforts to support and expand drug studies in children needs to be continued. And the framework, again, should anticipate and manage the tradeoffs that are going to be inherent in all medications between the drug's potential benefits and harms. And for some drugs, and this is, I think, somewhat unusual about opioids, is that those tradeoffs occur both for individual patients and potentially at a population level, because of the problem of how the drugs can be diverted and put into a situation where they could be misused.

So this is a little bit different than your typical case-by-case, what is the risk benefit tradeoff, and it's something to just be aware of, as you start to think about the challenges that I've tried to outline, in what I've said before, in labeling opioids.

Pediatric drug labeling should not be

looked upon as a solution for problems that labeling does not cause and cannot solve. Labeling can help drive clinical practice in effective directions, but it cannot solve problems that it has not caused, and it has neither caused nor can it solve them. Nor should it serve as a distraction and an excuse to not grapple with more effective solutions to stop the addiction of opioids epidemic.

In conclusion, our nation is facing an opioid epidemic that we need to stop. I want to be very clear that even though I come representing both of these groups, this statement is utterly true. We cannot shy away from the necessary steps that we need to take to effectively stop this disaster. At the same time, we need to serve and care for children with severe refractory pain, and that's our challenge that we have to develop a balanced policy to achieve both of these goals. Thank you.

DR. HUDAK: Thank you, Chris. I think we'll open the floor for any questions at this

point. Dr. Nelson?

DR. NELSON: Yes. That's fine, Mark. Let me just remind Committee Members that you did earlier, and welcome Ken, perhaps you want to say -- introduce yourself, Ken.

DR. TOWBIN: Good morning. I'm the late, Dr. Kenneth Towbin, I'm a Child and Adolescent Psychiatric in the Intramural Program and the National Institute of Mental Health.

DR. NELSON: So we are somehow channeling you, you are the late Dr. Towbin?

DR. TOWBIN: Would tardy be a better term?

DR. NELSON: (Laughter) Let me just remind the Members of Committee that this talk as well as the talk to follow were added to the agenda to set up the discussion in September, which is the Thursday, Friday, that's already been announced publicly, I think September 14th and 15th.

For that reason you were not screened for conflict of interest on opioids, so we would

encourage you to carefully restrict your questions to questions of clarification to whatever extent you slide into expressing opinions in the course of asking those questions you run the risk of being recused from the September meeting. So I would caution you to stay very closely to clarifying questions. But, yes, we can certainly ask clarifying questions for Chris, and then afterwards for the next presentation if you'd like to do that.

DR. HUDAK: Sure. So, just as a point of order again, please state your name when you ask your question, for the transcriber. Thank you.

DR. DRACKER: Bob Dracker. I was speaking to my colleagues last week, primarily because New York State is having, is taking a very strong position on restricting opioids use in both adults and children. But between 10 and 15 years ago, as physicians we were being told that we were grossly under-dosing patients with regards to the treatment of pain, and that we needed to not be as

fearful as we were at the time about using opioids for a multitude of patients, and it's very difficult for clinicians to know what to do, and how to do it. So I think your presentation is very useful, as long as we get better guidelines on how to deal with pain, and how to treat it more specifically.

DR. FEUDTNER: Let me just, in response to that questions make the observation that I've heard from many people around the United States that there is legislative or activity to try to figure out ways to curb the opioid misuse epidemic, and that there often is trying to curtail the ability to treat children who have severe chronic pain with opioids, as well as other children who may not need opioids. But the problem that we are confronting is that to try to close the one door of children who maybe don't need as much opioid or any opioid, we are really running the risk of closing the door of access to these very effective medications for groups of children who clearly need them.

And we have to be careful that we do not wind up closing the door to children who clearly need them. But that is not a problem that I see the FDA in a position to necessarily solve. I do see the FDA as being, potentially, caught up as one element in a solution, but I agree with you that we also need practice guidelines on how to take care of a wide variety of painful conditions, from things that are acute to things that are more chronic, where, perhaps play a role, or perhaps they do not play a role, and where opioids should appropriately play a role.

The other point that I will emphasize is, that I hear repeatedly, the difficulty of having the time to teach people how to manage their pain using all of the cognitive behavior techniques, all of the other mindfulness-based strategies that allow people to deal with levels of pain without needing to also rely on opioids, but that takes time, and it takes reimbursement.

So, again, that's not an FDA problem, and I call it out because I think that sometimes

the policy response is to, try to put too much emphasis that one piece of the overall solution puzzle, could solve the entire problem, and that is never going to give us the balance policy that we require.

DR. HUDAK: Dr. Davis?

DR. DAVIS: Jon Davis. I understand your thought process, part of the concern is in the United States within the last few years, it's I think now over a quarter billion prescriptions for opioid is written each year, 256 million we are up to, while the U.S. has 4 percent of the world's population, we write over 80 percent of the world's opioid prescriptions. I honestly believe that we fuel this opioid epidemic, and I think, you know, our colleagues' point about pain being the fifth vital sign, and JCAHOs real strong emphasis on that, probably help fuel this, but when you are in Europe and Asia they look at us oddly saying, we don't have this problem now.

Does that mean there's no children in the rest of the world with chronic pain, that

people aren't appropriately dealing with that? So, although I recognize that is a very strong need, I think, clearly, the public is looking to FDA, now what FDA is actually able to do in that area, is obviously going to be the subject for more discussion and debate and I know Dr. Califf's paper in the New England Journal outlined some of that.

But where would you suggest, I mean, because the physicians haven't been able to do this effectively I think that's why most States have now passed those laws. Massachusetts, for instance, you can't -- you can no longer prescribe opioids for more than 7 days, that's it, without special dispensation.

DR. FEUDTNER: Right.

DR. DAVIS: So how do we -- I think education is okay, but without some kind of mandate, especially when you have such disconnects with places like in the southern part of our country writing 150 opioid prescriptions for every person in the state.

DR. FEUDTNER: I think that your points are all very important to think through. First, there is the distinction between prescriptions going to adults and prescriptions going to children. And the statistics you cited are the statistics that are predominant, like way and above the majority for adults. Part of what we are seeing is that in our desire to protect adolescents, which I firmly believe, that is the group I'm here to advocate for, we are trying to be even more restrictive, ever more restrictive on the prescriptions going to pediatric patients, and then we offer the prescriptions going to the adult patients.

And to me, just thinking from a supply side, where most of the supply for illicit medications are going to come through family medicine cabinets, and through and illicit street trade, the majority of the pipeline that is feeding that illicit supply is going to adults, and yet our policy is backwards, we are trying to curtail pediatric prescriptions more than adult

prescriptions.

And again, I won't argue against some efforts at curtailment. I think that the challenge is to make sure that if you are a patient with cancer, a child with cancer, I'm going to leave this meeting and go back up to my hospital and take care of, unfortunately, several children like this, who are not going to succumb to that cancer and die in the next seven days, they will be in pain longer than seven days.

So, the challenge that we have to take very seriously is how do we make sure that we don't maroon those children without access to an ongoing necessary supply of a medicine that is proven to be effective for their pain, and at same time, take real steps to curtail the excessive prescriptions of opioids, but largely to a population that -- the adult population where it then gets diverted.

DR. NELSON: Mark, I need to step in here, please.

DR. HUDAK: Yes. Yes.

DR. NELSON: There has been -- I need to emphasize, neither one of those were clarifying questions, and so you do run the risk, when we get to the point of evaluating the September meeting to be recused from sitting around the table. So, there was in fact an internal discussion as to whether we should allow any clarifying questions because of the risk of people saying things, and not asking questions. So, I think we just need to move onto the next presentation.

And just to illustrate, with all due respect, clarifying a question would be: What is the Academy's position on the current use of opioids in the United States? Question, right, instead of an opinion, but we need -- there will be no more discussion at this point. No one has been cleared, there will be no more discussion, so let's move to the next presentation, and then you can ask the FDA, and then share and conduct all the questions that you want to make, but we cannot have discussion because you've not been cleared, period.

DR. HUDAK: Aye, aye. All right, our next presentation will be Dr. Sharon Hertz, who is Division Director, Division of Anesthesia, Analgesia, and Addiction Office of New Drugs, within CDER. And, Dr. Hertz?

DR. HERTZ: Thank you for the opportunity to be here this morning, and I'm sorry for tempting you with topics that are so high on the importance and restricting your discussion, but we want to make sure that we are set up for a very productive discussion in September, and I promise you'll have lots of time then for getting into this in-depth.

I've been working in the area of Analgesia at FDA for 17 years now, and throughout that time we've been working on trying to address some of the needs for pediatric patients. My next few slides are going to look very familiar to the folks on the Pediatric Advisory Committee, I'll go through them very quickly.

Obviously, we need studies because children should have access to medicines that's

been properly evaluated for them, and this can include clinical trials where there's a critical public health need. We just had a speaker from the AAP, this is a statement on the moral imperative for pediatric research, I won't read it, it's in your slides. Just to define, we are talking about children below the age of 17, but throughout the entire age spectrum. When we do studies we do develop cohorts based on the indication and the physiologic parameters such as enzyme maturation, or other considerations.

We've had a number of different legislative efforts to try and help fill gaps in pediatric information about drugs and other products regulated by FDA, this is just a few highlights of the legislation over the years. But back in '94, the concept of extrapolation was introduced into the legislation. We've had different legislation providing for different incentives include exclusivity over time.

We've also had legislation providing for additional safeguards for children in clinical

investigations. We consider them a special population, a vulnerable population and they are not treated same as adults in clinical trials as well as in -- they shouldn't be in, generally, in medicine. The two pieces of legislation that I think have been the most helpful in promoting clinical studies, including in my therapeutic area, BPCA, the Best Pharmaceuticals for Children's Act and PREA, the Pediatric Research Equity Act.

Just some of the differences, BPCA provides for voluntary pediatric drug assessments using a document called a written request, the written request specifies what studies are to be required, they can be clinical and non-clinical. These studies cover the moiety, not just the product, so they can span a number of indications, and it reflects what's considered to be a public health need. It also provides a process for studying products that are off-patent, for which companies may have less interest in evaluating, and it establishes that the Pediatric Review

Committee (PeRC) would review written requests prior to their issuance.

And that's a pretty rigorous process that anyone at FDA knows it's quite rigorous. So the process is generally for a sponsor to submit a proposed pediatric study request. Although we can issue a written request, even if a company does not request one, it allows for six months of marketing exclusivity, at times you see in slides referred to as the carrot. And we review these studies, the written requests are posted on the Web, and pediatric safety data will be presented publicly to an Advisory Committee a year after the studies are conducted. You folks will be very busy today doing some of this work.

PREA is a requirement that is imposed in certain settings. PREA is triggered by an application for new indication, new dosage form, new dosing regimen, new route for the administration, or a new active ingredient, and we spend a lot of time with this. It's an extremely important piece of legislation that's allowing us

to really, I think, in many therapeutic areas advance the understanding of these therapeutics for children.

We have criteria for waiving or deferring studies, and all of these plans and any waiver or referral requests are also discussed very extensively with PeRC. A few more landmarks, we will reauthorize for these legislations, these authorities in 2007, and even better, they've been made permanent as of 2012, along with some other extensions for other provisions.

Some of the concepts underlying pediatric studies have been captured in a guidance for industry, this is in ICH document in International Conference, a Harmonization document. I'm just going to run through the animation here. Just to say, this is a model of how we approach pediatric drug development based on the situation we decide if non-clinical studies, particularly juvenile non-clinical studies are necessary to anticipate potential toxicities, issues with development.

We can then take one of a couple of paths if we already have interest in developing the product for adults, we are typically going to phase one, often in healthy adults, but not always, followed by studies in adults with disease. If there is not a lot of interests in adult development, we still start with adults, because the one thing we don't allow is studying healthy children. As I mentioned before, children are a special population with special protections, and so that's not permitted.

And then ultimately we do studies in children with the disease. And which studies are done will depend on what we know about the disease, how it's expressed in children, and what we can expect for the mechanism of action of the drug, relative to a child's physiology and the condition.

Our current situation is, we have a pretty big unmet need for information in pediatric pain management. So while technically studies have been required since 2003 few studies have

been completed. Few products were labeled, and as you heard most used, certainly in my therapeutic area is off-label. This is a list of products that currently have some type of either -- And I'm sorry, it's small -- pediatric indication or labeling. So we have acetaminophen, aspirin ibuprofen, we have a variety of other nonsteroidal and inflammatory drugs that have a specific juvenile inflammatory arthritis indication, which provides a lot of interest if there is an interest, at dose in this for other conditions, these products.

There's only a few opioids though that actually have pediatric language in their labels, and as you can see it's fairly limited. We have some injectables, we have transdermal fentanyl with pyridine and the recently-labeled Oxycontin. We have a number of combination opioid, non-opioid products that have some pediatric language, and then the smaller font or just some lesser-used products that are for pain, for headache or other indications.

Here is a list of what doesn't have pediatric language that is approved for use in adults. It includes a variety of NSAIDs, other non-NSAID, non-opioid products and a long list of opioids, and opioid non-opioid combinations. This includes parenteral, oral, solid and liquid forms, immediate release and extended release forms, so there's a lot of gap in terms of how one could potentially use these products in appropriately-selected patients.

Prior to 2010 we, as a division, as part as part of an agency, were acquiring pharmacokinetic efficacy and safety studies for all pediatric analgesic programs, across the full spectrum of ages. We were getting very little progress. The sponsors were reluctant to try do studies according to our standard approach, and that include a lot of resistance to placebo-controlled trials, not hard to understand why.

We had a lot of difficulty with enrollment once the studies were -- stood up in

different programs. Parental reluctance, a lot of concern about harm to the children, concern about extensive blood work for PK information, ethical concerns. We use placebos in adults, adults can decide whether they want to participate in the placebo controlled study. We always make provisions for rescue in adult studies even, but that's a separate issue. But it's different with children.

And there is also concern about the risk of exposing children to more pain than they should be exposed to. We see relatively small populations, of pediatric pain, in terms of feasibility, for studies, and that's especially true for chronic pain. There is additional concerns beyond that for neonates, and the very young infant.

So we started trying to look for other ways to get information to try and help fill in some of these gaps, and we looked at the concept of extrapolation that has been introduced back in 1994, and here is the technical definition in the

course of the disease, if the course of the disease, and the effects of the drug are sufficiently similar in adults and pediatric patients, we may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients such pharmacokinetics PK studies.

So the reasons why this is important where it's appropriate is, I think fairly clear, particularly in this group, remember that patients, children are vulnerable, require the additional safeguards that have been mentioned, we very seriously look to try and minimize the number of children enrolled in studies, trying to get the most information possible from the least number of children exposed in clinical trials, so we try to make sure that they are very efficient and effectively designed.

We turn to outside experts to find out what the science was that could potentially

support an understanding of where extrapolation could be relevant in analgesics. So we convened a scientific workshop in 2009, and we invited experts in pediatric pain management clinical study design, ethics and drug development to come and discuss the sciences. It was not an advisory committee, we didn't ask for or receive advice, this was a discussion of the available science.

And we also asked for information about effective approaches to clinical study design, and you can all seize the outcomes, this was published ultimately in Pediatrics in 2012 by Chuck Berde, and that captures some of the discussion of the science that took place at that workshop. Based on what we heard, can be supported by the science. We went back and discussed this internally in terms of how to apply the current state of the science to pediatric programs in pain.

And what we decided on is that for opioids, nonsteroidals, anti-inflammatory drugs, NSAIDs, acetaminophen, and for local anesthetics when they are applied for pain. There is a basis

for understanding that we can extrapolate to a certain extent for efficacy, and we've decided that we would be able to support the science underlying extrapolation down to age 2, but below age 2, there was a lot of discussion about whether, given the state of the nervous system development it was fair to extrapolate further.

So, we get pharmacokinetic data and safety information, we don't extrapolate safety, for all age groups, and we are trying to get efficacy data for children below the age of 2.

Any other drug class were we don't have as much information or experience, we are still going to request a full range of studies for efficacy, safety, as well as the PK obviously. And we've discussed what chronic pain looks like in children within the Agency of a very long time, and what we've ultimately decided is, that although there are certainly patients less than 7, who experience chronic pain, the ability to conduct studies in that population is limited by the number. So we do permit waiving studies below

the age of 7.

When we do need to do a clinical trials for an analgesic rather than attempting to use the adult models for clinical trials we try to use an add-on design. So, basically the patients are treated according to standard of care, and then the study drug is added on, or a placebo is added, so it's a rigorous, randomized, controlled study, and because everyone is getting standard of care, no one should be experience any undue pain, but we can look at the reduction in the standard of care, often in opioid, but not always, as a measure of actually efficacy, so that it's a secondary effect, but if we already know that a product has analgesic effects in an adult, but we need to confirm that it's an analgesic in children, we use this type of model where we can.

This is particularly helpful, where we had neonates in infants, particularly where they are often managed using nurse or parent-controlled -- or patient- controlled analgesia, and that is often a source of our comparative data on the

amount of use.

It's not a useful for a product that has to be used as a standalone, but honestly, we just don't have much of that right now, in general, for analgesics. And yet industries continue in the struggle, so progress has been slow. Many of the same reasons still persists, numbers of patients, parental concern, reluctance of study sites, and it can take years, many years to complete a study, even what would be considered a relatively small one.

But we are pretty patient, if it takes years, then that's the answer in many cases, but we are frequently asked, particularly by sponsors or others that, you know, what is a reasonable period of time over which to conduct the study? And we don't have an absolute for that. I'm willing to wait, as there are many in the agency for a fairly long period of time, if it means we can get useful information, eventually.

Measurement remains an issue in pediatric studies, obviously the younger the child

the more difficult it is to self-report pain, pain is a patient-reported outcome; hard enough to get adults to accurately and consistently report their pain, so this becomes an issue particularly among nonverbal patients. We've addressed that in a couple of ways over the years, there have been some meetings, the Newborn Drug Development Initiative in 2003, and Pediatric Impact, it's a public-private partnership that we work as a part of back in 2005.

There are some references if you want to see some of the outcomes from those meetings, and in these meetings there was a discussion about outcome domains, and measures for children across, among other things, analgesic studies, and then discussion of some of the multidimensional indices that rely on behavior and physiologic responses, particularly in the very young.

So we have a number of instruments that can be used, and these have been discussed, it's important to make sure that the instruments chosen are relevant to the setting and have been

validated. We have folks at FDA whose job it is to work on validation and understand that, so we get a lot of assistance, but here are some of the instruments that are used.

Yes, this is a terrible slide, and it's terrible in your handouts and I apologize, but the good news is, it's all captured in the cited article. If you do have specific questions, this is a Chuck Berde article and it discusses a number of the infant pain scales that are available. Obviously evaluating pain in an infant is very challenging.

You heard that there has been some overall successes, for pediatric studies and labeling, and there's even results from some of the off-patent works starting to come in. So that's very exciting in a broad sense for pediatrics. We still need a lot of work in analgesics though, so we are using PREA everywhere it's appropriate. And we are encouraging BPCA as much as possible to use BPCA with a written request as much as possible.

I've already described the information that we generally seek for a lot of our products. This list, again, it's just a list, but we wanted to show you that we have a large number of pending PREA requirements. We take seriously the importance of having information, we think information is very powerful in terms of understanding how to manage children safely, and to make sure that the products can be expected to be effective, because it's always about the balance between efficacy and safety. If there is no expectation of efficacy, then there is no justification for risk.

Now, the bigger issue of opioids and the intersect with children, we have been working with the rest of our partners in HHS, on a number of initiatives trying to address the national problem of prescription opioids use. Our Commissioner, our new Commissioner, Dr. Califf recently announced an FDA Opioid Action Plan, and I'll spend a little bit of time going through this, and again, we can discuss this more, particularly as

it pertains to children in September.

We are going to be reexamining the risk-benefit paradigm with regard to the wider public health effects. Now, this is not something we are going to begin to do, this is something that we do always, we've been aware of the growing problem of prescription opioid abuse for almost as long as I have been here at FDA, and we have been trying to work on what we can within our regulatory authority, to try and improve labeling which is our primary communication tools, with prescribers, and any other efforts we have risk evaluation and mitigations strategies that we set up.

I encourage you to attend or listen to our May meeting, where we will be discussing a large class, REMS, for extended release and long-acting opioids. So that's coming up in May. And we heard very loudly that there was a lot of concern about not prospectively taking some of our products to Committee prior to approval, so we will be seeing you folks, as well as others, more

frequently in the future.

And we also recently announced a very massive labeling effort to update the large and varied number of immediate release opioids products. This is a very heavy lift, we are happy to have the opportunity to finally roll up our sleeves and start doing this. That was announced just a couple weeks ago, and we work very carefully and closely with industry to try and promote the development of safer formulations. These abuse deterrent opioids are intended to restrict manipulation for the purposes of abuse.

There are some additional benefits for some of these formulations, and possibly helping to avoid unintended by chewing and dose dumping, things like that for some of the products, but the primary focus is to make them less appealing for abuse. There are some very interesting novel approaches understand development that I hope will come to fruition. We are applying all of the authorities we have to help facilitate and expedite these programs.

We are working very hard with sponsors to facilitate development of naloxone formulations that are suitable for use in the community. There's been a lot of off-label use of naloxone, but it's variable across the country depending on different programs. We've approved two products, an auto-injector, and this past fall, a nasal spray that reliably delivery a dose of naloxone that meets the standard that was set in a variety of public meetings where this was discussed.

Basically we have good quality pharmacokinetic data that show these formulations to get an early and substantial naloxone exposure. These do include pediatric labeling to some extent based on consideration of pediatric dosing that was in the original naloxone labels as well as other considerations. We are also trying to do what we can to help facilitate development of medication-assisted treatments.

And of course we support better pain management options, and including non-pharmacologic treatments, not particularly

under our regulatory authority. We are working very hard to facilitate development of non-opioid analgesic alternatives and there's a couple of new drug classes that are very exciting, not free of risk, but potentially very exciting, and we are working hard to help facilitate that development.

We recently had a meeting of the FDA's Science Board, this is an advisory committee the agency level, and we discussed a number of relevant topics for the crisis that we are having right now, including the role of opioids in pain management, some of the scientific challenges that we face in developing non-opioid products. Challenges to understanding what's really happening in the real world situation of managing pain, treating pain and using opioids that -- or products that have potentially less risk for abuse.

We are working to try and coordinate efforts across the department, as well as working with state and local environments to try and do what we can to help. We have a tremendous, it

really should be largest font, perhaps, or a much bigger font to emphasize the amount of work that's being done by our safety group on the post-market surveillance activities related to opioid use, misuse and abuse.

We actually have definitions inside the Agency that differ a little bit from outside for how we distinguish those, and trying to understand proper use, misuse, which would in our area, we would consider the situation where someone takes more than prescribed, trying to get more of the therapeutic effect, or mistakenly thinks they can share their analgesic with someone else who is having pain.

And then we have, of course, the problem of abuse which we refer the attempt to get high, the psychological reinforcing effects we refer to. And we use those distinctions to help us sort through a variety of different data sources, but the Office of Surveillance and Epidemiology in our division had been working quite a bit on these efforts.

So I mentioned that May 3rd and 4th, we have a two-day meeting to discuss this risk-evaluation and mitigation strategy that we put in place for the extended release of long-acting opioids back in 2012. There is a primary focus to look and see if the REMs is meeting certain criteria that were stipulated in the law that gave us that authority, but beyond that we are going to be discussing broader issues about risk mitigation for opioids.

I think it's going to be a really robust discussion, and I encourage folks to try and attend or listen. And then of course we have the September meeting coming up, and I want to emphasize that this is going to be a very important meeting, for a variety of reasons. First of all, it's three committees that we are bringing together to tackle some of these issues, and provide advice to us. We have my division home committee, if you will, the Anesthetic and Analgesic Drug Products Advisory Committee, where we've been discussion a lot of issues associated

with drug development programs, abuse-deterrent opioids as well as many of the safety issues.

We have the Drug, Safety and Risk Management Advisory Committee, because you really can't discuss and opioid with now discussing and taking into consideration, all of the safety issues and the public health impacts of any decisions that are made. And we are inviting you folks back because we need your expertise with this very special patient population, and to help guide us as we tackle some of these questions.

So we are going to discuss, what is an appropriate development plan for the safety and efficacy of prescriptions opioids in pediatric patients, analgesics not other opioids, and including the PK data that we obtained, and the use of extrapolation. So we are going to revisit that with you and the other committees. We are going to have some potentially interesting data that we hope to be able to share, to help guide the discussion.

This is a little unusual for us, but I

think very important. If we have a docket open for public comments, it's already open in advance of the September meeting, because obviously this is a very charged topic, we have a lot people with very strong opinions about different aspects that we will be covering, so we've opened the docket to accept input from the public.

There's a citation for the docket on the slide, and that docket was started, it was opened in February, and we'll continue to just past -- a couple weeks past the Advisory Committee for any last-minute thoughts. So, I want to thank you in advance for your thoughts about this in September, I want you to know that we are trying to balance the important needs of the patient with the important needs of the public health. It's a challenging thing to do.

FDA does participate in a number of efforts. I just want to mention, we work with an interagency Pain Research Coordination Committee that was established under the Affordable Care Act, where we have participated in the development

of the National Pain Strategy. If you are not familiar with that document, it's I think a very important discussion with input from several agencies, FDA, NIH, CDC and others, and about what we think are important areas to consider as we consider, or think about pain in this country, and we were also working on the National Pain Research Strategy to try and stimulate and support research in areas where there are gaps.

So, once again, thank you for your time and attention, and I look forward to reading your comments in our docket, and we will read every comment, and to your participation in September. Thank you.

DR. HUDAK: Thank you, Dr. Hertz. That was a very good presentation. The FDA has taken a very thoughtful approach over the years to the scientific questions underlying some of these medications, and it's nice to hear the plans in the future, for really, sort of bringing home, some of the safety and efficacy information. And I also want to thank Dr. Feudtner from the AAP for

giving a very good overview of some of the issues in pediatric.

I think that everybody, or almost everybody, around this table, as a pediatric provider, occasionally, or frequently taking care of some of these patients with chronic complex diseases; and understands well the balance that we need to achieve between individual population issues and the appropriate care of the individual patients. So thank you very much for that.

And I will turn it over, I think, to Marieann to make some comments about the open public hearing.

MS. BRILL: Well, we will start with our open public hearing, and Dr. Hudak will read a statement about the open public hearing.

(Open Public Hearing)

DR. HUDAK: So, I believe we have two registered public speakers today, and basically some remarks for the record here, are that the FDA and the public believe in a transparent process for information gathering and decision-making, and

to ensure this transparency of this open public session, the FDA believes it is important to understand the context of an individual's presentation. So this reason the FDA encourages you, the open public hearing speaker, at the beginning of your statement to, please advise of any financial relationship that you may have with any firm or any group, their products and if known, their direct competitors that are likely to be impacted by the topic you address in your presentation today.

For example, this financial information may include the payment of your travel, lodging and other expenses in connection with your attendance at this meeting. Likewise FDA encourages you at the beginning of the statement to advise us if you don't have such a financial relationship. If you choose not to address this issue of financial relationship at the beginning of your statement; it will not preclude you from your speaking.

So, in an effort to maintain

transparencies, we like to have copies of speakers' statements available. I think the first speaker does have a statement available. I'm not sure that the second speaker does at this time, but maybe we can request that. And these statements are on display at the registration table outside the meeting. Some of the statements made have been redacted in order to protect any personal or private information that may have been included. So our first speaker today that was registered was a Mr. Butler; and if he could come to the microphone. Thank you.

MS. BRILL: I'm sorry. Before you start, please state your name, and also state any current or previous financial involvement, like what Hudak said, with any firm whose product you may wish to comment on. You will have 5 minutes to speak. And after you state and your affiliation, we will start with the timer. Thank you. Hold on a second, please.

DR. HUDAK: We've reset the clock.

MR. BUTLER: My name is Craig Butler,

I'm the National Executive Director for the Cooley's Anemia Foundation, and I do not have any financial relationships to disclose.

DR. HUDAK: Okay.

MR. BUTLER: I would like to thank you for the opportunity to address the Committee this morning. I'm here today to follow up on a matter which we raised at this Committee's meeting on September 16, 2015, specifically the need for a label change for the iron chelator Exjade, concerning cessation during times of febrile illness, and the need for continued monitoring of this medication among the pediatric population.

As the Foundation mentioned during its appearance here last fall, we are motivated to request these actions due to the tragic passing in January 2015, of Zayna Connolly, a thalassemia patient shortly before her third birthday. While the circumstances which brought about the sudden death are complicated, the fact that a high fever was present during a period when the child was receiving chelation therapy via Exjade is

troubling and has raised significant concern among the thalassemia population, especially among parents of young children.

As you know, regular and consistent iron chelation therapy is crucial to the long-term health outcomes of people with thalassemia. This is complicated by the fact that there is no one ideal chelator which works equally well for all patients, and by the fact that each chelator has features which may limit its use in any individual patient. Many patients and parents, express concern about remaining on Exjade after Zayna's passing, but may have felt that other options are not viable for them; it is therefore crucial that these patients and parents feel safe with the chelated option.

Proper guidance in administration of the drug is essential for this to happen. There is currently no specific guidance on the Exjade label about whether to halt administration temporarily for fever-related illnesses. On the label for Exjade, fever is listed as a possible side effect

of the drug, and while, in general, drugs may be discontinued due to side effects, this does not address the proper paths to take when dealing with a fever that is not caused by the chelator itself. And since children are prone to frequent illnesses that may be accompanied by a fever, a clarification of if or when chelation should be suspended is crucial.

Beyond the issue of febrile illness and chelating use, we encourage the FDA to continue safety monitoring of Exjade, in the pediatric population. The availability of Exjade as an oral chelating option, has resulted in significant, positive change for many people living with thalassemia. However, the lack of a large U.S. Thalassemia population makes it difficult to obtain data, especially in a specific subset such as pediatric patients of an already small patient population.

This is true of both preapproval and post-marketing studies and reports, and such being the case, it's crucial that post-marketing data be

examined especially carefully. We know that the FDA does an exceptional job in this area and only request that special attention be paid to pediatric patients on Exjade. For our part we are continuing to educate or patient population about the need to report adverse events, related to any area of thalassemia care.

We know that the more information the FDA receives the more effectively it can provide appropriate monitoring. We know that this Committee has listened to our request, and appreciate the commitment to action in this area. Please note that the Foundation is thankful for your attention and response, your willingness to recommend that the FDA investigate and appropriate course of action, is appreciated by us and by the patients we represent, and we gratefully acknowledge communications from Dr. Judith Cope that assure that the FDA is planning a follow up to the Committee on the issues we raised.

We now would request the timeline for further action, and to be appraised of what steps

are being taken in these areas. We wish to reiterate that the Foundation is willing to provide assistance in whatever way it can to help the FDA's work forward on this matter. Thank you for listening.

DR. HUDAK: Thank you, Mr. Butler. Dr. Cope are you willing to make some comment?

DR. COPE: Yes. Thank you, Mr. Butler. Yes. FDA does understand the concerns of the transfusion-dependent community, and we actually are using all available resources to develop a clear response to the families that use Exjade. The FDA review is currently in process and we do plan to publicly present these findings at a future PAC. Thank you.

Now I also do want to thank you for bringing up your education or your Foundation educating the patients for the need to report adverse events. That's always important as everybody knows the pediatric population, it may be vulnerable in different ways than the other age groups, and even one adverse event is a piece to

the puzzle that FDA, you know, put together as we look at all the adverse events, and look for safety signals.

So, again, we do want to thank you and we are planning to publicly present the findings of the ongoing work that is being done will be going to a future PAC.

DR. NELSON: Yes, we just wanted, for the record, to note two comments that we had received through email, one I think you can mention, and I'll briefly summarize the second, we received at 9:30 p.m. last night.

DR. HUDAK: Right. So the first public comment apparently surrounded the use of vaccine in children, and basically we acknowledged receiving comments from an individual who raised concerns on the use of vaccines. That person is not here to present. And then, as you said, Dr. Nelson, the second was a more lengthy communication.

(Public open hearing closed.)

DR. NELSON: Yes. I think some members

of the Committee, not all, have received -- you may not even have checked your email at 9:30 last night, an email from Mr. Andrew Thibault, Parents against Pharmaceutical Abuse, talking about Vyvanse. Expressing concerns about the framing, if you will, of the adverse events reported in the Vyvanse review, and a rather lengthy discussing of other documents as part of that.

At the end of the day there were no specific labeling, recommendations or any differences than the current labeling, but I've asked, that some of you receive that for review. We have limited printing capabilities, I'm hoping I can at least print out one copy so Ken can look at that prior to the discussion of Vyvanse this afternoon, but I'm not sure, technically, if we've been able to accomplish that yet.

MS. WEINEL: Yes.

DR. HUDAK: Oops. We have. So you can look at that between now and when Vyvanse is on the agenda this afternoon, to see if you think any further comments are useful. And for the record,

obviously, this was also sent to the members of the Division of Pharmacoepidemiology -- Pharmacovigilance, and they'll obviously take into consideration whether these comments merit a sort of reevaluation of our approach to that product. But I don't think there's a reason to get into it now, since it's on the agenda after lunch today.

DR. TOWBIN: I would only say that I did not receive this email, so thank you for printing this out, and I'm happy to look it over.

DR. NELSON: I notice it didn't go to everybody, I guess it's whomever emails were found through Internet Googling, since I don't think we list emails on our agenda.

DR. HUDAK: Okay. Thank you. So we are about an hour ahead of schedule, so I will take my Chairman's prerogative, and with Dr. Quinto being here --

MS. WEINEL: We can take a break now, it's time for a break.

DR. HUDAK: No. I understand, but I'd like to move on with Dr. Quinto's presentation, if

that's okay?

MS. WEINEL: Yes.

DR. HUDAK: All right. Just to sort of move up some time; so he is here and able and willing; so, Dr. Quinto, if you would, introduce yourself briefly to the group?

DR. QUINTO: Good morning. My name is Lieutenant Commander Kenneth Quinto. I'm a Medical Officer in the Officer of Pediatric Therapeutics.

I will be presenting the products from the Center of Biologics Evaluation and Research, CBER. Just for background, all three CBER products presented today are vaccines, and all our presentations, all the presentations will be abbreviated. Just to remind you, CBER abbreviated presentations mean that the full review was performed. With vaccines, the safety report utilize the various database, a vaccine adverse events database administered by both the FDA and CDC.

After the full review, the vaccines met

the criteria for an abbreviated presentation format, because there were no new safety signals recognized. There were no reports specifically of pediatric deaths that would be attributed to the vaccine. The FDA would see that the product could go back to continued routine monitoring.

The first vaccine is the FluLaval Quadrivalent vaccine. It is the active immunization for prevention of influenza disease, caused by influenza A, subtype viruses, and type B viruses that are contained in the vaccine. The initiation of this pediatric post marketing safety review, was August 15, 2013, approval of FluLaval Quadrivalent vaccine in persons 3 years and older.

Based on the background material you receive the plan would be that FDA will continue its ongoing standard safety monitoring. Does the Committee concur?

DR. HUDAK: So, open up for questions.

DR. NELSON: Mark, we someone from the FDA who has joined the table, we may want to introduce.

DR. HUDAK: Oh. Please, yes, introduce yourself. I missed your arrival.

DR. ZINDERMAN: Craig Zinderman, I'm Associate Director for Product Safety in the Office of Biostatistics and Epidemiology in the Center for Biologics.

DR. HUDAK: Thank you. Questions? All right, hearing none, we can vote on the question, does the Committee concur with continuing standard ongoing safety monitoring for the FluLaval Quadrivalent influenza virus vaccine? Ms. Celento?

MS. CELENTO: No. That's okay. Sorry.

DR. HUDAK: Okay. So, we'll take a show of hands, I believe, to start with. All in favor?

DR. CUNNINGHAM: We can vote using the microphone?

DR. HUDAK: Yeah. Okay, so we'll go around the room, and everybody announce their name and their vote for the record.

DR. WALKER-HARDING: Leslie Walker-Harding. Yes, I concur.

DR. TURER: Christy Turer. Yes, I concur.

DR. BAKER: Susan Baker. I concur.

DR. KASKEL: Rick Kaskel. I concur.

DR. MINK: John Mink. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. WHITE: Michael White. I concur.

MS. CELENTO: Amy Celento. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin, concur.

DR. DAVIS: Jonathan Davis. I concur.

DR. MOON: Marc Moon. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. CNAAN: Avital Cnaan. I concur.

(Committee concurs with FDA's view, passed unanimously. No nays.)

DR. HUDAK: Okay. We'll move onto the next vaccine presentation.

DR. QUINTO: Next, we are at FluLaval. FluLaval is a trivalent version of the FluLaval Quadrivalent in the previous slide. FluLaval is an active immunization for the prevention of influenza, for type A sub-viruses, and type B virus.

The initiation of this pediatric post-marketing safety review was August 16, 2013 approval of FluLaval for expanded age usage in persons 3 years and older. Again, no safety signals were found by the FDA, and there were no reports of pediatric deaths that were felt to be attributed to the vaccine. So with that, the FDA would continue its standard, ongoing safety monitoring. Does the Committee concur?

DR. HUDAK: Any questions or discussion? Again, hearing none, we'll vote by show hands. All those in favor of continuing standard monitoring? All right, we'll go around the table starting with Dr. Cnaan, first.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. MOON: Marc Moon. I concur.

DR. DAVIS: Jonathan Davis. I concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. HAVENS: Peter Havens. I concur.

MS. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. MINK: John Mink. I concur.

DR. KASKEL: Rick Kaskel. I concur.

DR. BAKER: Susan Baker. I concur.

DR. TURER: Christy Turer. Yes, I concur.

DR. WALKER-HARDING: Leslie Walker-Harding. I concur.

(Committee unanimously concurs with FDA's view.)

DR. HUDAK: Very good, so we will proceed to the third vaccine, Fluzone.

DR. QUINTO: Lastly, we have Fluzone Quadrivalent. Fluzone Quadrivalent is an active immunization for the prevention of influenza for type A subtype viruses, and type B viruses. The initiation of this pediatric post-marketing safety review, was a June 7, 2013 approval, of Fluzone Quadrivalent for the use in persons 6 months and older. Again, no safety signals were found by the FDA, and there were no reports of pediatric deaths that were felt to be attributed to the vaccine. The FDA would continue its standard ongoing safety monitoring. Does the Committee concur?

DR. HUDAK: Okay. Again, we'll vote on the question by show of hands. All in favor? All right, we go around the room in this order?

DR. WALKER-HARDING: Leslie Walker. I concur.

DR. TURER: Christy Turer. Yes, I

concur.

DR. BAKER: Susan Baker. I concur.

DR. KASKEL: Rick Kaskel. I concur.

DR. MINK: John Mink. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. WHITE: Michael White. I concur.

MS. CELENTO: Amy Celento, concur.

DR. HAVENS: Peter Havens. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. DAVIS: Jonathan Davis. I concur.

DR. MOON: Marc Moon. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. CNAAN: Avital Cnaan. I concur.

(Committee concurs with FDA's view, passed unanimously. No nays.)

DR. HUDAK: Very good. Thank you, Dr.

Quinto.

DR. QUINTO: Thank you.

DR. HUDAK: So, I have been advised that with the gastronomic priorities of getting the lunch forms in, we are going to take a 15-minute break compile those forms and do other things, and we will gather back at 10:00 o'clock, at which we will still be one hour ahead of schedule, so there is hope for a non-working lunch in fact, perhaps. Early lunch.

DR. NELSON: Early finish.

DR. HUDAK: Early finish. Okay. Is that the vote of the Committee?

DR. NELSON: Yes.

DR. HUDAK: Okay. All right, very good. Thank you. Be back at 10:00 o'clock.

(Recess)

DR. HUDAK: I'd like to get started in the interest of time, in the interest of getting out early.

MS. BRILL: Excuse me. I'd like to make an announcement before we convene. Our lunches

will be picked up at the Harmony Room, it's right next to our front desk, at 12:00 o'clock today. Thank you.

DR. HUDAK: Okay. I'd like to just sort of provide some clarification on the schedule of events for today. We've done some reordering, so we will -- for those of you who have access to an agenda, we will do the presentations, the abbreviated presentations on SKYLA and Xeloda, followed by the standard review on Mycamine and Noxafil. And we'll go directly then, to presentation on Precedex and Aciphex Sprinkle, and then we will be at our working lunch at 12:30.

So, a couple of other things; I have just received a technical orientation to the full functionality of the equipment in front of you, so there are in fact voting buttons here that are labeled "yes" and "no" so at the end of -- What's that?

MS. BRILL: And abstain.

DR. HUDAK: And abstain, but nobody ever abstains, right, though rarely. So you can press

"yes" "no" or "abstain" we will not do a show of hands. We will not go around the room, we'll just ask for a vote and it will apparently display, magically, upon the screen, I'm told, some bar graph presentation of yes and no, so you'll know whether you are in the majority or in the minority, without any pre-bias. So we will get started. I think for -- Yes, Skip?

DR. NELSON: I think though for the purposes of the transcript, after the vote we still go around if I'm not mistaken. It's displayed -- it eliminates the show of hands, but we still go around the room so the transcript indicates the vote of the individual.

DR. HUDAK: Is that correct? You don't have the technical capacity to sort download the numbers and people to the yes and no category?

DR. NELSON: Yes. Two separate issues.

DR. HUDAK: All right. I'm still getting educated, maybe by the end of my term I'll have this job down.

DR. NELSON: I don't know about that

Mark. We'll change the rules on you at some point.

DR. HUDAK: Thank you, Skip. All right, so for -- Okay, so now this is the next two presentations, they've been moved up, so people who aren't necessarily here, they'll be some people participating by phone, so I'll try to get this straightened out. So, Dr. Cope is going to present about SKYLA, we have one representative from FDA at the table.

MS. KANG: Sarah Kang from Division of Pharmacovigilance. I'm Safety Evaluator.

DR. HUDAK: Thank you. And then do we have anybody on the phone for this presentation, FDA experts?

DR. ORLEANS: Ron Orleans, a Medical Officer in DBRUP.

DR. SOULE: I'm Lisa Soule, Clinical Team Leader in DBRUP, and Rita Ouellet-Hellstrom from OSE-Epi.

DR. HUDAK: Very good. Okay. So I think, Judy, we are ready to get started.

(

DR. COPE: Okay. So I'll get started then with SKYLA, so the next two presentations that I'll do are abbreviated. SKYLA is levonorgestrel-releasing intrauterine system. You all have received the full safety and drug utilization review that was conducted. It's in your background materials. Basically SKYLA was first approved in January of 2013 for use in adolescents, that's post-menarche, and adults which prompted this mandate of pediatric post-market review.

And it's indicated for contraception, prevention of pregnancy for up to three years. It's a small intrauterine system, T-shaped polyethylene frame and it contains 13.5 milligrams of levonorgestrel. So when the full safety and use review was done, here is what was found:

Unique adverse events; serious events, no deaths between April 4, 2013, through August 31, 2015. And below what I've listed here are the different types of Serious Adverse Events (SAEs),

so there was one or two events that had more than one adverse event. So there were cases of expulsion, 11 of those, four with altered bleeding which many of you know, is expected with this type of medication, and two pregnancies, and one pelvic inflammatory disease. And I might mention all of these, the expulsion, the bleeding the pregnancy and the PID is mentioned in the warning and precautions of the label which was mentioned in your safety review.

Regarding the drug utilization review, for the pediatric patient age group 0-17, was 6 percent, so that was 1,583 out of 26,915 total patients. And again, as mentioned in the footnote below, these are data obtained from a sample of pharmacies, clinics, hospitals and physician offices.

So this full safety and use review did not bring up any new safety signals, and so the FDA sees that we recommend continuing standard, ongoing safety monitoring. And does the Committee concur? We would ask that you vote, or discuss,

and both.

DR. HUDAK: Okay. So we'll open for discussion.

DR. HOEHN: Sarah Hoehn. I have a question, like a clarifying question. Is there a younger age limit, or a minimum weight?

DR. COPE: No. Not that I'm aware of. Menarche, it says in the label that, you know, these are to be used in girls that have menarche. I think the youngest in this -- in these adverse events was most all were 13 to 17 years of age, and you know, as you know menarches usually are at age 12.5 years.

DR. HOEHN: I have a follow-up question. Is there a minimum number of periods they have to have before they can have it put in?

DR. COPE: I can let the Division answer that, I don't think that's in the label.

DR. SOULE: Hi. This is Lisa Soule, there's no minimum number of periods.

DR. HUDAK: Dr. Towbin?

DR. TOWBIN: I just wanted to make a

comment that I really appreciate how clearly the label spells out MRI Safety. For those of us that do a great deal of magnetic resonance imaging, not all labels are as clearly spelled out as this one, and I appreciate that we've kept up with the times, because there are circumstances where this information is necessary, and it's great that it's in the label rather than having to search around somewhere on a website for it. So, thank you very much.

DR. TURER: Christy Turer. I had concerns regarding there being an absence of bone mineral density data in any children under 17. So I understand that this 1,600 were in clinical use, but in fact there are no studies that examine bone mineral density data. And extrapolating from the Depo-Provera data, there appears to be a substantial impact of these contraceptives that lack estrogen on having an adverse impact on bone over time.

DR. COPE: I don't have any comments. I don't know if the Division wants to.

DR. ORLEANS: There is some data from the pivotal studies but not abstract.....

DR. SOULE: And I think in general, with Depo-Provera, it was not so much that we saw a differential effect on adolescent bones, it was more concern about failing to recover and obviously a much higher systemic response.

DR. TURER: Christy Turer again. There is a good deal of data though, correct me if I'm wrong, Dr. Cope, regarding bone building in this age group, that may be different from adults. Correct? That your peak bone mass is building in the adolescent years, that might warrant consideration, looking at this specifically in adolescents.

DR. COPE: Yes. I mean, I'm not sure on that. I don't know where the bone mineral density would vary according to where you are. You know, Tanner stages, and menarche, and I mean, everybody's spine doesn't finish growing until the 20s, but I'm so sure. I mean the growth plates and all finish, pretty much, I think in girls by

menarche, but I can be corrected on that. I'm not so sure.

DR. SOULE: This is a Lisa Soule again. I think, again, you are correct, that we don't have direct dates in adolescence, but the systemic levels of LNG with SKYLA are very low. And we have not seen signals of concern from adult data.

DR. NELSON: Yes. Just so people on the -- I think we heard that last comment, and so what I heard was that the actual blood levels of the medication are low, and in the case of SKYLA, and would not necessarily then be as concerning as it might have been in Depo-Provera. But unfortunately, just so the Division knows, we were unable to really hear well what you said earlier about Depo-Provera, so if you wanted to repeat that, do it slowly, because the phone connection is not ideal.

DR. TURER: Christy Turer again. So, there have published data regarding the effects of hormonal contraception on bone mineral density after 24 months of use, and what was noted is that

women who are taking medroxyprogesterone acetate, which doesn't have estrogen, compared to those who are on contraception, that has both estrogen component and a progesterone component, and cause about 5.7 percent loss in bone mineral density, with a 3.2 percent loss occurring between months 12 and 24.

Subsequent studies looked at the impact of estrogen replacement therapy in long-term users, and it does appear to rescue this response. But I'd have concern, just because we have such a paucity of data of the impact of our drugs in children on adult health. What's the impact of putting adolescents on a progesterone-only contraception, on bone health, you know, in their 40s and their 50s? Might we see a signal of increased fracture risk, given that we are hitting them with this, at the time of peak bone mass accumulation?

DR. SOULE: This is Lisa Soule, again, and I'll try to speak slowly.

The systemic exposure with Skyla is much

lower than it is with Depo-Provera. In the adult Skyla Bone Mineral Density (BMD) data, there was no decrease in BMD.

DR. SOULE: I'm sorry, there was no decease in density.

DR. HUDAK: So, if I understand that correctly, the data that are available in adults show no decrease in bone density. The actual measurements of levels, in adolescence show very low levels in the blood, and in terms of answering the question as to whether there are long-term effects, I don't know to what extent, FDA is able to address that question.

DR. SOULE: I think we are unable to address the question of long-term effects.

DR. NELSON: If I might point out, we are having a whole two-day meeting starting tomorrow as a workshop on doing long-term safety studies in pediatrics, which are a challenge.

DR. COPE: That's a good point.

DR. HUDAK: Exactly. Yes?

DR. WALKER-HARDING: So, I'm curious

because we do know -- I mean the adult data would not even correlate to the adolescent woman --

Female data who is laying bone. You know, there are many, many studies looking in Depo-Provera, I wasn't overly concerned given the low amount that are in these IUDs, because this isn't the only one, IUDs or progesterone, but if -- Are people not going to study it in adolescents because we can't use the adult data to compare that to adolescents.

DR. HUDAK: For the record, that was Dr. Walker-Harding. And, anybody at the FDA wants to respond to that?

DR. NELSON: Let me clarify the question then. And this is Skip Nelson, to clarify the question. The observation, I guess, or hypothesis is that adolescents -- the impact on adolescent bone would be different than the impact on adult bone. Given that at the time that they may well be growing and laying down a bone, which I think intuitively makes sense. I guess what's not clear to me is the extent to which SKYLA, per se, would

be implicated in that, given the blood levels, which is a very different issue than whether or not there should be broader studies if things like Depo-Provera on that question.

So it would be helpful to be able to distinguish the level of concern relative to this product, per se, versus a more general statement that bone health in adolescents on progesterone only contraceptive, is something that the Agency should consider in the future and it looks at other products, so that will be helpful to have some clarification of your concern.

DR. TURER: Yes. Christy Turer. To clarify, it would be a broader concern, not with this product only, but progestin-only contraceptive in adolescents.

DR. NELSON: Obviously not with this product only, with the blood levels though that are low, be reassuring that in fact for this product such a study would be unnecessary, or not?

DR. TURER: I cannot determine that from the data.

DR. HUDAK: Okay. So I think that we have an unanswerable question at the moment that may require more data for FDA to consider how that might be addressed under the current regulatory structures. But for the moment, I guess, we will vote on the question of: Should FDA continue a standard ongoing safety monitoring for this product?

DR. NELSON: I pressed my button and something suddenly it's starting to flash. Can you -- Let them keep flashing. So, just to be clear, we've heard the concerns, we can certainly engage in conversation with the division around contraceptives, studies of adolescent contraceptives are always interesting and challenging. As you can imagine given that population the extrapolation of efficacy from adults to children, and carry that conversation forward which would separate from deciding whether or not, for SKYLA, per se, there needs to be any changes in how we go about the adverse event, monitoring, which would not answer the question

you are asking. So I just wanted to be clear that by voting yes on this question you are not saying that we wouldn't think about the issue that you've raised.

DR. HUDAK: Okay. So we will proceed with the new button technology here, yes, no or abstain. Okay. So, we will go around the room, starting with this side of the room, and register or votes orally.

DR. WALKER-HARDING: Leslie Walker, concur.

DR. TURER: Christy Turer, abstain.

DR. BAKER: Susan Baker. I concur.

DR. KASKEL: Rick Kaskel, concur.

DR. MINK: John Mink, concur.

DR. CUNNINGHAM: Melody Cunningham, concur.

DR. HOEHN: Sarah Hoehn, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. WHITE: Michael White, concur.

MS. CELENTO: Amy Celento, concur. And

I just want to thank Skip for your comments prior to the vote, because that made it a lot easier to ensure that there will be follow up even if we vote, that we want routine safety in monitoring. Thank you.

DR. HAVENS: Peter Havens, concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin, concur.

DR. DAVIS: Jonathan Davis, concur.

DR. MOON: Marc Moon, concur.

DR. DRACKER: Bob Dracker, concur.

DR. CNAAN: Avital Cnaan, concur.

(FDA view agreed. No Nays. Dr. Turer abstains.)

DR. HUDAK: Okay, so for the record then, the Committee has voted in a great majority to continue routine surveillance, safety surveillance for SKYLA, which is a separate process in looking forward to any potential long-Term effects on bone density, and the young adulthood in later years. Judy you are ready to go the second presentation on Xeloda?

DR. COPE: Sure. So, we'll move on to another abbreviated presentation, Xeloda. Again, the full safety and drug utilization was provided --

DR. HUDAK: Excuse me. Judy, let me --

DR. COPE: Oh. I'm sorry.

DR. HUDAK: I made an error. So let me welcome to the table, and have them introduce themselves, the FDA experts in this area. And then after they introduce themselves, if there's anybody potentially on the phone, if they could announce themselves as well. Thank you.

DR. REAMAN: Gregory Reaman, from the Office of Hematology and Oncology Products.

DR. RAND: Margaret Rand, Safety Evaluator and Division of Pharmacovigilance.

DR. HUDAK: Any one on the phone. Okay, nobody. Thank you.

DR. COPE: Okay. So we'll start with Xeloda. Now Xeloda was first approved in 1998, indicated for adjuvant colon cancer, metastatic colorectal cancer, and metastatic breast cancer.

And overall the safety and effectiveness in children has not been established. So, basically there were two trials in pediatric patients with newly-diagnosed brain stem gliomas, and high-grade gliomas. And that review, or those studies did not find that Xeloda was safe and effective in pediatric patients.

So, there is no pediatric indication at this point, but that's what prompted this review to come before the Committee. The safety in use review basically revealed serious adverse events, over several years from 1998 through August of 2015, there were three deaths due to disease progression, so those kids had, you know, excess chemotherapy and one had an infection and died, and then there were 13 non-fatal serious adverse events, and most of them were in the Xeloda clinical trial studies that had been carried out.

There were also three in-utero exposures, I think there were two of those that had air anomalies, one accidental exposure, and then there were three reports with the labeled

events as you see here. And then there were six reports with unlabeled events, including four CNS necrosis, one intracranial hemorrhage and one child with amnesia.

The pediatric population as far as use accounted, was very, very low, so they were basically in this drug utilization review that were like 36 patients. So again, you know, pretty much the trials, it's not really being used. And that use actually was over four years from September 2011 through August 2015.

So, overall, there really wasn't any new safety signals, that FDA identified, very little use and many of these serious adverse events and deaths were due to the underlying disease or disease progression. Most of the -- Or many of the events were labeled, and FDA saw that the product labeling is appropriate. So, we recommend continuing its standard, ongoing safety monitoring for Xeloda, and we ask whether the Committee concurs?

DR. HUDAK: Thank you, Dr. Cope. Do we

have other, new people? We've introduced them, they've introduced themselves. Okay. Thank you. All right, so we open it up for question, discussion, comment.

DR. RAKOWSKY: Alex Rakowsky, just a clarifying question. So, most of those adverse events came from that study that was done in pediatrics, or is that off-label, reported use --

DR. COPE: No. Most of them I think are but -- about half of them came from the two clinical trials.

DR. RAND: I can speak to that as well. Ten of the patients were from the Oklahoma study group, there were two colon cancer patients, and the rest were the accidental exposure, and the in-utero exposure.

DR. HUDAK: Dr. Walker-Harding?

DR. WALKER-HARDING: I was just curious, is there any anticipation that this will be used in pediatric sedations? You said there were 36, which means that somebody felt it was an indication. Is it anticipated, this one increase?

DR. REAMAN: I can address that; there's no plans, and probably no real consideration that it will be used. It was evaluated initially because of the fact that it was a drug that crossed the blood-brain barrier, and hence the evaluation in brain tumors in the two studies which Dr. Cope mentioned. It very much like another drug that is used in both adult and pediatric oncology, 5-Fluorouracil or so, and there would be no reason to use capecitabine in lieu of that.

DR. HUDAK: Okay. I think we will do the voting. Again, the button is yes, no, or abstain. Okay. So we will go around the room, starting with Dr. Cnaan.

DR. CNAAN: I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. MOON: Marc Moon. I concur.

DR. DAVIS: Jonathan Davis. I concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. HAVENS: Peter Havens. I concur.

MS. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White. I concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. HOEHN: Sarah Hoehn, I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. MINK: John Mink, concur.

DR. KASKEL: Rick Kaskel, I concur.

DR. BAKER: Susan Baker. I concur.

DR. TURER: Christy Turer. I concur.

DR. WALKER-HARDING: Leslie Walker-Harding, concur.

(Committee concurs with FDA's views on Xeloda. No nays voiced)

DR. HUDAK: Okay. Thank you. We will move on to another presentation, and I'm not sure if Dr. Radden is here.

MS. WEINEL: Yes.

DR. HUDAK: Excellent. Okay. So, we will proceed with Dr. Radden, from the Division of Pediatric and Maternal Health. Office of New Drug

at CDER giving a standard review on Mycamine, which is micafungin, and I'm just asking if there's anybody else in the room, if the FDA wants to -- Yes. Two people, can introduce themselves. Thank you.

Dr. YASINSKAYA: This is Yuliya Yasinskaya, Medical Officer from the Division of Anti-Infective Products.

DR. MATTHEW: Justin Mathew, Drug Utilization Analyst.

DR. HUDAK: Okay. Dr. Radden.

DR. RADDEN: All right. I'm used to having this behind me but okay. So, today I'll be presenting the safety review for Mycamine or Micafungin. And I'll following this outline shown here, starting with some background information. Mycamine is an Echinocandin, indicated for patients 4 months of age, and older, for various invasive candida infections, and for prophylaxis of candida in patients undergoing hematopoietic stem cell transplantation, or HSCT.

Mycamine is approved for intravenous

infusion, at doses ranging from 50 to 150 milligrams daily in adults, and 1 to 3 milligrams per kilogram per day in pediatric patients. Mycamine was originally approved in March 2005, and in June 2013, approval for all of the indications, was extended down to patients four months of age, which triggered this review.

Efficacy for Mycamine for all the approved indications, was extrapolated from adequate and well controlled trials, in adults. This extrapolation was also supported by PK data in 229 pediatric patients. In addition to safety data from 479 pediatric patients, who received doses ranging from 0.75 to 10 milligrams per kilogram per day. Data from two clinical trials conducted in adults and pediatric patients for the treatment of invasive candidiasis and candidemia prophylaxis of candida infections in patients undergoing HSCT, also supported the efficacy and safety of Mycamine, for the approved population.

The label and change is associated with this approval, include changes to the pediatric

use subsection, 8.4, which describes of safety and effectness have been demonstrated in patients 4 months of age, older, but not in patients less than 4 months of age. Additionally, pediatric PK dosing, adverse reactions, and clinical trial data were included throughout labeling.

Now let's look at the use of Mycamine. This figure shows the number of pediatric patients, age zero to 12 years, who had a hospital billing from micafungin from the U.S. non-federal hospital setting, from September 2010 through August 2015. As you can see the overall number of pediatric patients, age zero to 16 years, more than doubled, throughout the exam and time period. During the most recent 12-month period, from September 2014 through August 2015, of the nearly 4,000 patients approximately 58 percent were age 0 to 11 years, about 29 percent were age 12 to 16 years, and percent were zero to 1 year.

Now let's turn our attention to the safety and pediatric-focused adverse even associated with Mycamine. You will notice that of

the 108 events reported for pediatric patients since the original approval of the product, 103 were classified as serious, with 50 deaths.

Now I'll walk you through these reports of serious and fatal events. Recall that 103 reports were deemed serious with 50 death, 81 cases including 38 deaths were excluded for the reasons noted here, including complications associated with underlying conditions, duplicate reports, labeled events, and insufficient data to assess causality. That left us with 22 cases including 12 deaths and 10 serious unlabeled events.

This slide shows a summary of the 22 adverse events in this case series including 12 fatal events. Ten patients experienced non-fatal unlabeled adverse events, which are listed here, including various hematologic, renal, hepatic and neurologic conditions. Note that all of these unlabeled events were only reported once, but some of these case reports include more than one event.

So, first I'll discuss the fatal events.

The 12 fatal events were reported in patients from birth to 14 years of age, include five preterm neonates. All the deaths involved highly immunocompromised patients, with complicated clinical courses associated with invasive fungal disease, prematurity, complications, post-bone marrow transplant, or pneumonia.

Additionally, the patients were being treated with various immunosuppressive agents, antibiotics and corticosteroids. A comprehensive review of these cases found that these events were related to underlying concurrent disease processes. Concomitant medications, or other coincidental factors. Ultimately, there was no reasonable basis to conclude causality. Furthermore, many of the reported events were closely related to labeled events.

You will notice a similar overall pattern with the serious unlabeled events which I will discuss next. The 10 reports with serious unlabeled adverse events involved patients 10 days to 15 years of age who, again, were highly

immunocompromised with complicated clinical courses involving, leukemia, prematurity, HSCT, cardiac surgery, hepatic carcinoma, lupus and myelodysplastic syndrome. These patients were also taking various immunosuppressants, antibiotics and corticosteroids.

These cases were highly confounded, for example, by underlying disease processes, or provided limited or insufficient data to assess causality. Additionally, those specific patterns of adverse events was noted. And this concludes the pediatric-focused safety review.

As a result of this recent approval, Mycamine is indicated in patients 4 months of age and older, and our review found the cases to be highly confounded, or with insufficient information to assess causality. No new safety signals were identified, and the FDA recommends continued ongoing surveillance. Does the Committee concur?

And I'd like to acknowledge the assistance of my colleagues noted on this slide.

DR. HUDAK: Thank you, Dr. Radden. We are open for questions. Dr. Cnaan, you got your hand up first.

DR. CNAAN: Yes. Dr. Radden, can you go back, please, to slide 10. So, I'm trying to understand the excluded versus included. And in the excluded there are two categories that -- Let me back up. Are those that are included those that required additional review? Is that why you are focusing on these 22?

DR. RADDEN: I'll let our Safety Reviewer comment.

DR. HAUSMAN: Yes. Hi. This is Ethan Hausman from Pediatric and Maternal Health. We'll let the folks from OSE take over, but when the cases are excluded they are actually reviewed and excluded for the reasons listed, and you'll see that modification on the later presentations, so it's not that they fit a bunch of criteria, and nobody looks at them further. The cases are all read and adjudicated by the folks in Pharmacovigilance. And I'm going to defer over to

OSE now.

DR. CAO: Yes. Kelly Cao, Safety Evaluated Team Leader from the Division of Pharmacovigilance. The cases that were excluded were excluded either because they were duplicates, or after review they were clearly related to the underlying disease state, or they were labeled events that are known to occur, so the focus of the case series was really on serious unlabeled adverse events to determine if there were any new safety signals. But all of the cases were reviewed in detail.

DR. CNAAN: Okay. This is Avital Cnaan again. It was sort of a two-part question, so therefore the total doesn't reflect any quantity of interest in its own right, since you are excluding all of those events which are already-labeled events, and that's fine. What is then the difference between the cases that are excluded for insufficient clinical information for causality, versus the cases that are included, that also say, insufficient clinical information

for causality, in the more detailed narrative? What's the difference between those two?

DR. CAO: Kelly Cao from Pharmacovigilance. Yes. There was a fine line between the two. It really came down to, you know, professional judgment, but if you looked at the cases that were given as examples, you would see that, in general, because there was no safety signal identified, the cases -- the amount of data in the cases was far less than the cases we excluded, compared to even the ones that you saw the description within the case series.

So there was some judgment involved in deciding whether there was -- Some of the cases, for example, may have just reported the adverse event and not provided any clinical details, so those cases, for example, were probably excluded. The ones that were included we at least had some information, although it might not have complete information.

DR. CNAAN: Thank you.

DR. HAVENS: In clinical practice the

doses that are used are dramatically different than the labeled doses, and varied by patient age, from very milligram per kilogram doses in the youngest children, to lower milligram per kilogram doses in older children. Does FDA have the capability of looking at that dosage use data, and associating that with adverse events, or not?

DR. CAO: Yes. I'm Kelly again. If the cases did provide a dosage, and I believe they were provided, but we may not have put it on this table, but we did gather that information, and look to see if the adverse events may have been related to higher doses than what's labeled, and we didn't notice anything unusual about that, so we didn't bring that up. But we do evaluate that on a regular basis. We looked at the dosage and the adverse events to see if, maybe, there was some association there, like higher doses may lead to more adverse events.

DR. HAVENS: And since higher doses are so common now in clinical practice, is there a standardized approach to monitoring that? Or is

that impossible to do at the level of the FDA?

DR. CAO: In terms of post-marketing adverse event reports, when we receive the reports we do look to see what the dosage is, and if there was an overdose we do take that into account. There isn't any prospective work that we do, and no active surveillance, but with the reports that are coming in we do evaluate that closely.

DR. HUDAK: That question came from Dr. Havens, for the record. And Dr. Hoehn, you are next in queue.

DR. HOEHN: Sarah Hoehn. I had a question about the data, the completeness of the data, and some of the case series that were reported, they talked about like autopsy ongoing from 2011. So I don't know what the follow up was in terms of getting autopsy reports and things like that. I don't know if that makes sense.

DR. CAO: Sure. Yes. At the time the reports were received that was -- what the information was provided, and we do seek follow up in many of our reports but, you know, we select

which reports we attempt to receive follow up on. It will be reports that we think are pretty compelling, but it's just missing some vital information, but if the reports seems to be pretty clear, that the adverse event or adverse outcome was clearly related to some underlying disease then we may not seek follow up in those particular cases.

DR. HOEHN: Thank you.

DR. HUDAK: Dr. Davis has a question.

DR. DAVIS: So when you are describing deaths related to prematurity and clearly the drugs being used in a preterm population without necessarily -- I don't believe it's FDA approved for use in prenates, are there opportunities -- I mean, we are just getting the tip of the iceberg, we don't know often it's being used, and how it's being reported to you, associated with the drug versus just general prematurity. Are there opportunities for FDA via some mechanism, written request, or others, to ask for that to be studied or examined in more detail in premature infants?

Dr. YASINSKAYA: This is Yuliya Yasinskaya, Medical Officer from the Division of Anti-Infective. We currently have pediatric written request, of which four studies have already resulted in pediatric labeling. There is one study is outstanding for neonatal population, so children zero to 3 months of age. You know, the sponsor is still collecting the data, even though the study having problems in enrolling the patients, but this data is being collected.

DR. HUDAK: Seeing no further questions, we can proceed to the vote which is -- Put that slide back up. Does the Committee concur with FDA's recommendation to continue ongoing surveillance? We appear to have a good response, so we'll go around the room starting with Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. MOON: Dr. Moon. I concur.

DR. DAVIS: Jon Davis. I concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. HAVENS: Peter Havens. I concur.

MS. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White, concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. HOEHN: Sarah Hoehn, concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. MINK: John Mink, concur.

DR. KASKEL: Rick Kaskel, concur.

DR. BAKER: Susan Baker, concur.

DR. TURER: Christy Turer, concur.

DR. WALKER-HARDING: Leslie Walker-Harding, concur.

(Committee concurs unanimously with FDA's recommendation for continuous surveillance.)

DR. HUDAK: Let the record reflect that the Committee unanimously supports the continued ongoing surveillance for Mycamine. So do I see Dr. Taylor? Thank you. Dr. Taylor is coming to

the podium. She's going to talk about Noxafil. And she is in the Division of Maternal and Pediatric Health, of the Office of New Drugs, CDER. And do we have new visitors to the table from the FDA, who can introduce themselves? I see two.

DR. REAMAN: Gregory Reaman, from the Office of Hematology and Oncology Products.

DR. O'SHAUGHNESSY: Elizabeth O'Shaughnessy from the Division of Anti-Infective Products.

DR. JANCEL: Timothy Jancel, Division of Pharmacovigilance.

DR. HUDAK: Thank you. And we do appreciate you changing your schedule to deal with our accelerated agenda this morning.

DR. TAYLOR: Thank you. I will be presenting the pediatric focused safety review for Noxafil, or posaconazole. This is the outline for my presentation. I'll begin with the background information. Noxafil has been marketed since September 2006, the approval of the delayed

release tablets initiated the safety review.

Noxafil is indicated for prophylaxis of invasive aspergillus and candida infections, and for the treatment of oropharyngeal candidiasis. There are several counter indications which are listed here, as well as several warnings and precautions listed on this slide and on the next slide.

I will next discuss the pediatric studies. Approval of the delayed release tablets was based on bridging studies in adults, the use of posaconazole oral suspension and delayed release tablets in children, is supported by adequate and well-controlled studies in adults, as well as PK safety and bioavailability studies in adults.

No new pediatric studies were conducted to support approval of the tablets in pediatric patients. There were two previously conducted pediatric studies, the first was in 12 patients, 13 to 17 years old, given posaconazole oral suspension for prophylaxis of invasive fungal

infections. The second was of 16 patients, 8 to 17 years old, treated with posaconazole for another indication.

Next I will discuss drug utilization trends. This figure shows the number of pediatric patients aged zero to 12 years, who had hospital discharge billing for all posaconazole, from the U.S. non-federal hospital setting. The overall number of pediatric patients age zero to 17 years, doubled through the examined time period, from September 2010 through August 2015. The spike in pediatric patients during the 12-month time period from September 2012 through August 2013, may be attributed to a small sample size.

During the most recent 12-month period from September 2014 to August 2015, approximately 67 percent or 170 patients were age 13 to 17 years, while 33 percent or 85 patients were age zero to 12 years.

I will now review the FAERS safety cases. There were a total 105 pediatric reports 90 of which were considered serious with 18

deaths. All reports were reviewed, 56 reports were excluded for the reasons shown here. This leaves us with a case series of 34 cases, including 13 deaths.

These are some of the characteristics of the case series. There were 13 cases with a fatal outcome. All 13 cases involved patients who were very ill, and on multiple drugs. I show one example case here. This is a case of 10 year-old female with aplastic anemia who developed a fungal -- an invasive fungal infection. The patient improved on anti-fungal treatment, including posaconazole. She received a hematopoietic stem cell transplant, which unfortunately failed.

She later received a second transplant. Six weeks later she developed a disseminated adenovirus infection, which led to her death. There were 10 cases reporting a drug interaction involving posaconazole and vincristine. Of note, some of the cases involve more than one associated event. We should note here that posaconazole is a strong inhibitor of CYP3A4, and is labeled for a

potential drug interaction with vincristine. Vincristine is also labeled for caution with use of posaconazole and other strong CYP3A inhibitors.

These are the additional unlabeled adverse events associated with 11 cases. Some cases have more than one associated adverse event. This concludes the pediatric focus safety review, our FAERS reports. There is a safety signal of posaconazole, vincristine drug interaction. FDA is evaluating the safety signal to determine if and how labeling may be modified, and we'll provide a report to the PAC at a future meeting. Following this evaluation FDA recommends continuing routine, ongoing post-marketing safety monitoring. Does the Committee concur?

And I would like to thank the following people shown here for their help with this presentation.

DR. HUDAK: Okay. This is open for discussion. Dr. Rakowsky?

DR. RAKOWSKY: Alex Rakowsky. So the current label under 710 for vinca alkaloids, most

of the vinca alkaloids, substrates of CYP3A4, posaconazole may increase the plasma concentrations of vinca alkaloids elements as vincristine, which will lead to neurotoxicity. And then the line is therefore the recommended dosage of the vinca alkaloids be considered. So what kind of labeling change would you consider? Something very specific in terms of, if you are using vincristine then decrease a range? Or, what do you envision as a potential change based on this data?

DR. TAYLOR: I guess Dr. Hausman wants to answer that?

DR. HAUSMAN: Yes. Right now, it's a little premature to get into the details of what we'd recommend since the review is ongoing. It could be any number of different things, and I wouldn't want to have anybody accidentally put FDA in a position where we would be unintentionally promising something.

DR. RAKOWSKY: If I can't just follow up on that. So what's the labeling precedent in

terms of what kind of specificity you can put in that kind of -- like it's for a specific drug?

DR. NELSON: I can't speak to specifics, maybe the Division can. But I think the point is that we would strengthen in that direction, so whatever labeling wording is arrived at would be a strengthening of that concern, but if Greg or -- This is Skip Nelson -- If Greg or --

DR. REAMAN: I can speak on behalf of the vincristine dose. I think there might be consideration of avoiding the use of posaconazole when vincristine is part of a chemotherapy regimen. Because I'm not sure that we would want to sacrifice the therapeutic efficacy of vincristine if there are alternative antifungal therapies that could be used. But, again, as Dr. Hausman mentioned, that will come up at the review.

DR. HUDAK: Dr. Dracker?

DR. DRACKER: Bob Dracker, I was just going to say the same thing. The priority is treating the primary disorder with

chemotherapeutic agent; the treatments -- options for a fungal infection, or others to consider, actually; and so I agree that the dosage and the consideration drug should be secondary issues, not the first.

DR. HUDAK: Dr. Towbin?

DR. TOWBIN: I just had a question. Would the label come back to this Committee once the language has been decided?

DR. NELSON: We discuss how to word the recommendations that you are voting on, and this is what we arrived at, and hopefully it's clear. But the intent would be that once the report is completed which would include a labeling recommendation, that would come back to the Committee at a future PAC meeting. I don't want to assume how long that will take, but I would hope it would not take that long.

So, yes, you would see that report and so in voting yes here, you are really -- it's a compound vote. One, yes means (a) the report comes back to you with the labeling

recommendation, you are certainly welcome at that point to comment on whether you think that's suitable or not; (b) it would be routine monitoring at that point, but doing what we are doing now with the label is not routine, which is why we put: following this evaluation. I hope that's clear. If it's not, I'm happy to wordsmith it.

DR. TOWBIN: This is Kenneth Towbin. Again, just in follow up. Skip, you are always very clear, and that was a clear answer. I think, if I could just voice a request here, that if the concern has to do with the CYP metabolism, that as the label currently reflects, there are a bunch of different agents that go through that pathway, and so vincristine, of course, is one but there could be a host of others, and I would request that that be made very clear to people so that anything that uses that pathway would be a concern.

DR. HUDAK: Dr. Taylor, I did have one question for you. You were in a slide, very quickly, that spoke about interaction with

Midazolam? If I read that correctly; was that an earlier slide?

DR. TAYLOR: Oh. Yes. Under warnings and precautions.

DR. HUDAK: Right. So, the question I have is whether or not there's been any data on adverse events in patients that might be on both Noxafil and midazolam, and if not, how would FDA look at this, because I can envision several situations where patients might receive these medications concurrently?

DR. TAYLOR: I don't know if the Division of Anti- Infective wanted to comment.

DR. O'SHAUGHNESSY: Actually we haven't looked at that data, but now that you suggest it, I think we could incorporate that into the safety, that we are looking at for vincristine, just add that on, and have a look at it.

DR. ALEXANDER: So I would say that the increase with midazolam is something that's noted specifically within the labeling, again, the issue of the drug and its known effects on CYP3A

inhibitions. So the question would be, if we saw anything from the -- I don't think there was anything specific noted with the OSE review for pediatrics.

DR. O'SHAUGHNESSY: There wasn't anything specific, but I guess we could always look and make sure there is nothing.

DR. HUDAK: Okay. Oh. Yes. Dr Moon?

DR. MOON: And the midazolam, is there other agents like midazolam, and there's lots of variations on that, so you can't specifically only look at midazolam.

DR. ALEXANDER: Understood, it did include other benzodiazepine, the issue with midazolam being pointed out is actually because it was something that was seen in midazolam is often used as a drug for sort evaluating drug interactions.

DR. HUDAK: All right. We will open this up for voting then. Again, a yes vote is to concur with FDA's recommendation to continue routine, ongoing safety monitoring.

DR. RAKOWSKY: Can I clarify quickly? Alex Rakowsky. So this is concurring the continuing the monitoring with the caveat that there is going to be work on the label, which they'll come back, potentially? So it's a double question there.

DR. HUDAK: Yes.

DR. NELSON: A yes vote is answering yes to both that, we are going to do the report, we'll add midazolam, and we'll bring that back to the PAC, and that routine monitoring would be the sort of order of the day at that point. And of course, since you'll be seeing the report, if you thought that was in appropriate then, you'll always have a chance to say, well, on second thought there's something else you might want to do. If anyone thinks they want to vote on one or the other, we can divide the question, but we put it together thinking that it was a package.

DR. HUDAK: I was going to vote separately on each of those questions, but what's the sense of the Committee?

DR. NELSON: Feel free to do that if you'd like to, Mark.

DR. HUDAK: Okay. We will vote just on the routine monitoring, the question first. Okay. Again, we have a unanimous consensus to continue routine monitoring. I guess for the record we still need to go around the room, and we'll start with Dr. Walker-Harding.

DR. WALKER-HARDING: Leslie Walker, concur.

DR. TURER: Christy Turer, concur.

DR. BAKER: Susan Baker, concur.

DR. KASKEL: Rick Kaskel, concur.

DR. MINK: John Mink, concur.

DR. CUNNINGHAM: Melody Cunningham, concur.

DR. HOEHN: Sarah Hoehn, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. WHITE: Michael White, concur.

MS. CELENTO: Amy Celento, concur.

DR. HAVENS: Peter Havens, concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin. I concur with ongoing monitoring.

DR. DAVIS: Jonathan Davis, concur.

DR. MOON: Marc Moon, concur.

DR. DRACKER: Bob Dracker, concur.

DR. CNAAN: Avital Cnaan, concur.

(FDA concurs unanimously to continue routine monitoring.)

DR. HUDAK: All right. Then we'll vote on the second motion, the Committee is in agreement with, or not, with the FDA's plan to focus on interaction with vincristine and to bring additional information forward for consideration of label evolution. Okay. Again, we have unanimous decision. We'll go around the room, starting with Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. MOON: Marc Moon. I concur.

DR. DAVIS: Jonathan Davis, concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.
DR. HAVENS: Peter Havens, concur.
MS. CELENTO: Amy Celento, concur.
DR. WHITE: Michael White, concur.
DR. CAMPBELL: Jeff Campbell, concur.
DR. CATALETTO: Mary Cataletto, concur.
DR. HOEHN: Sarah Hoehn, concur.
DR. CUNNINGHAM: Melody Cunningham, concur.
DR. MINK: John Mink. I concur.
DR. KASKEL: Rick Kaskel, concur.
DR. BAKER: Susan Baker, concur.
DR. TURER: Christy Turer, concur.
DR. WALKER-HARDING: Leslie Walker-Harding, concur.
(Committee unanimously concurs with FDA's view on vincristine.)
DR. HUDAK: Very good. So, Dr. Taylor, you still have the floor. Do we have anybody else from FDA on the product Precedex, that would like to come to the table and introduce themselves? I'm searching the audience. Yes, maybe? So we

give people a minute to regroup here.

DR. POLLOCK: Martin Pollock, Drug Safety Evaluator.

DR. WONG: Jennie Wong, Drug Utilization Analyst.

DR. CRISAFI: Leah Crisafi, Acting Clinical Team Leader, Division of Anesthesia, Analgesia and Addiction Products.

DR. ROCA: I'm Rigoberto Roca, I'm Deputy Division Director in the Division of Anesthesia, Analgesia and Addiction Products.

DR. HUDAK: Okay. So, Dr. Taylor, I'm looking forward to your discussion because we are seeing more and more of this medication being used in the NICUs.

DR. TAYLOR: This is a safety review for Precedex, or dexmedetomidine. This is the outline for my presentation. I will start with background information. Precedex is marketed as an injection. It was originally approved for marketing on December 17th, 1999. Precedex is approved for sedation of ventilated patients

during treatment in an ICU or non-intubated patients for surgical or other procedures. There are no pediatric indications.

This slide lists the warning and precautions included in the labeling. Next I will focus on the pediatric studies. These three studies on this slide initiated today's review. There was one assessor-blinded trial and two open label studies in the pediatric age group to assess efficacy for ICU sedation. These studies did not meet their primary efficacy endpoint. The safety data were insufficient to fully characterize the safety profile of Precedex for pediatric patients. A description of the studies conducted, and the lack of studies for procedural sedation was added to the labeling in Section 8.4.

Next I will focus on the drug use trends. Approximately 571,000 patients received a hospital billing for dexmedetomidine during the most recent 12-month period. Pediatric patients accounted for 18 percent of the total patients. This graph provides the number of pediatric

patients with a hospital billing for Precedex, from U.S. Non-federal hospital, stratified by age.

During the most recent 12-month period ending in May 2015, approximately 104,000 patients age zero to 16 years, received a hospital billing for dexmedetomidine. Patients aged 2 to 11 years accounted for the largest proportion of users.

I will next focus on the FAERS safety case series. The total number of reports for pediatrics was 69, with 56 reporting as serious event. There were two reports of death. All pediatric reports were evaluated, 19 duplicate reports were excluded leaving a case series of 37 including two deaths.

These are some of the characteristics of the case series. There were two fatal cases. The first involves a ten-year-old with Rett Syndrome and scoliosis surgery. She developed severe hypotension and bradycardia within 20 to 30 minutes after dexmedetomidine.

The second case involved a 15-day-old,

premature infant with multiple comorbidities. One day after receiving dexmedetomidine, and ultra-sound showed decreased cardiac flow, bradycardia, and left ventricular hypertrophy. The patient subsequently died. His dexmedetomidine level was elevated. This case is confounded by comorbidities, and multiple medications.

The next series of slides present the serious, nonfatal adverse events by system organ class. The unlabeled events are underlined. Of note, in many of these cases, the patients had other medications and comorbidities. Details of the cases are in the Office of Surveillance and Epidemiology Review.

These are the cardiovascular events. These are the neuropsychiatric events. Some of these events were associated with withdrawal of dexmedetomidine.

Here we have the medication errors, and the related clinical events, as well as the hypersensitivity events, and then other events.

This concludes the pediatric-focused

safety review FAERS reports. There are no new safety signals identified. FDA recommends continuing routine ongoing post-marketing safety monitoring. Does the Committee concur?

And I'd like to thank these folks for helping me with this presentation.

DR. HUDAK: All right. We're open for discussion. Dr. White second.

DR. HOEHN: I have a question about the two deaths. I find it difficult to interpret the data without knowing the dose, because it seems like it would make a difference if they had, perhaps, received ten times the dose versus the regular dose. So it was hard for me to interpret those deaths without knowing what the order of dose was, what the range was. It just says, "unknown dose."

So I didn't know if there was any follow up or any way to looking into either what dose was ordered, what dose was documented, what dose was in the pump, because it seems like that that's important information interpreting these two

deaths, particularly, the older one.

DR. TAYLOR: Dr. Pollock. I don't know if you want --

DR. POLLOCK: Yeah, where it says an unknown dose, we did not do follow up in a number of cases as far as what the dose is. We just -- we reported it as unknown. You're concerned -- there are two deaths. Both of them you're concerned about?

DR. HOEHN: Correct. I had concerns about both of them. Mainly, with the first one where the child received CPR within 30 minutes of the initiation of the dose in a ten-year-old.

DR. POLLOCK: Yeah, with the Rett Syndrome, right, that patient?

DR. HOEHN: Correct. Is there a way for the Committee to request follow up? I just don't know how to interpret two deaths if we don't know what dose was given.

DR. HAUSMAN: Hi, this is Ethan Hausman. The Committee, of course, can request what it feels is necessary to help make a

decision. The lack of dosing may or may not be a resolvable issue in the end. Sometimes when reports go into Medwatch and ARS, there's a limitation of data because the reporting person or entity does not have the information.

So I will leave it to OSE to determine if there's any ability to get more information on the specific cases. But this is a scenario that highlights some of the limitations of our passive reporting system.

DR. POLLOCK: I just want to say one thing about the second case. You that, the review over there. Whatever the dose was, it appears to be that it was confounded with other drugs over there, reporting there's a levopromazine, Sufentanil. So there were other agents present also, but I don't know if there was any confounders on the first disclosure, no.

DR. HUDAK: Dr. Cunningham.

DR. CUNNINGHAM: Thank you. Melody Cunningham. I was just wondering, you said that some of the serious adverse events were due to

withdrawal, and clinically I've seen that, and often those patients are transitioned onto Clonidine before coming off of their Precedex if they've been on for a long time.

Is there any request for how long after a patient comes off of Precedex that they're monitored? Because it seems like the majority of information is when they're on the medication, but certainly their withdrawal can be serious in terms of what you would expect for sedation withdrawal systems, but also significant tachycardia.

DR. TAYLOR: Would the Division like to respond to that?

DR. ROCA: At this point, we don't have -- I apologize. We don't on that at this point. We're certainly going to be aware of any new events coming in and looking into things like that and if possible request the information. But at this point, I don't have any comment for you.

DR. HUDAK: Dr. Draker.

DR. DRAKER: Bob Draker. This is, I think, a good example of a drug that would do very

well with a pediatric clinical trial. When you compare this with other drugs are used like Ketamine, and some of the others for procedures like bone marrows and others, it just looks like a great drug. Very short half-life, very few side effects, and I think it would be very useful for us trying to do procedures in children.

DR. HUDAK: Dr. Nelson.

DR. NELSON: Let me make a few remarks to broaden the context here that people may want to comment on, and the Division may want to comment on.

You know, members of the Committee that have been around a while certainly are familiar with the discussion over the years of the neuroapoptosis as a result of inhalational anesthetics and other sedatives that are administered in children, certainly, in the juvenile animal models, and the concern that that may, in fact, be a signal that is potentially real in infants, young infants, below, say, two or three years of age.

And so I think part of the interest in dexmedetomidine is generated by the possibility that the thought is that may not have as much of an effect, although there is a lot of discussion about the need to do juvenile animal modeling, and juvenile animal studies to actually document that or not, and there are trials that are being done under IND on dexmedetomidine by academic investigators, and there's a lot of discussion about how to design a clinical trial that would potentially look at anesthetic sparing regimes in a long enough exposure that would allow one to be able to say that a certain approach to anesthesia would be safer. The data doesn't exist at this point, and part of the challenge is taking a medication such as dexmedetomidine which is more a sedative than an actual anesthetic, and giving that to an infant who needs a procedure that's four hours long, which is what the animal data would suggest the exposure needs to be.

And then just one final comment. I mean, there is a public/private partnership called

SmartTots which is dedicated to try to sort this out. But it's a very challenging area to get both the study design sorted out, but also to figure out who's going to fund that once it is.

And there have been some studies. I think the GAS study was actually published, if I recall, or at least it's public, that looked at regional approaches to inguinal hernia repair versus general anesthetic approaches, but the difficulty there -- and didn't see a difference, but the problem is that's only a one-hour exposure, and the animal data would suggest you need at least a three or four-hour exposure to be able to get any change.

And so, yes. You're absolutely right that there is hopes that something like this product may be useful, but the data are in evolution and need to be gathered. So just for a lot of big context around this product.

DR. HUDAK: Okay. I'm going to go around the room in this order because I don't know -- well, I'll do Dr. White first because he had

his hand up earlier and then never commented.

DR. WHITE: I'm going to do my best to channel Dr. Rosenthal. I'll be clinically correct. Not very good at that, but I'll try.

I wanted to point out that one of the great accomplishments of the opposite pediatric therapeutics is getting through PREA, and all the regulations that allow us to do drug requests. And then I want to point out the problem that Precedex has presented, which if you look at the clinical review here, there are three studies, and they were total failures because the data submitted was completely useless.

This is a drug that we have found somewhere between 13 and 19 percent of total patients that receive Precedex are under the age of 17, and over half of those are under, like, the age of 12 in the data that we have. And we have no useful data, and no label for this drug.

Is there a mechanism when this written request fails for us to get the drug company to perform the studies that we need? That's the real

question that is raised in my mind when I look at this clinical review that we've got which the studies were there. They were done under written request, and the data was gathered in such a fashion that it wasn't useful.

DR. NELSON: Skip Nelson. So written requests, as you know, are voluntary, so there's no way we could get the sponsor to do them unless they were interested in doing voluntary studies. We can issue a second written request that's rarely done, and if we did that, it could be picked up potentially by NICHD under BPCA to do that.

The challenge though there is most of the studies that they're doing are often smaller sort of Phase 1 - 2 dosing studies, and what's really needed here is a big clinical study that's well conducted with an appropriate control group, and I can reassure you that there is a lot of conversation going on within the pediatric anesthesia community about what such a study should look at that's involving European,

Canadian, U.S., and Australian colleagues.

So there's an attempt do that, but I don't think the BPCA mechanism would probably be very effective at doing that.

DR. HUDAK: Thank you. Dr. Hoehn, then Dr. Mink.

DR. HOEHN: Sarah Hoehn. Given that rampant use of this drug everywhere we saw on the numbers, I didn't know if there was a choice other than yes or no. If there's something you can vote for that's a higher level of monitoring instead of routine monitoring, especially given the lack of details on the two deaths.

DR. NELSON: Let me start an answer to that, and then see if others have comments. Part of the challenges is asking what's the question. I mean, certainly one can follow up on a death and make an assessment of causality relative to dosing effect. Information would or wouldn't be available. That happens to be a labeled event, and in the clinical studies that are going on, you see kids getting hypertensive -- cardiac arrest

within 30 minutes is unacceptable from a clinical perspective.

The challenge is the routine monitoring is a passive event reporting system, and if what's really necessary are some of the conversations we're having around appropriately designed pediatric clinical trials, there's nothing you can do to our post-marketing safety monitoring that's going to answer that question.

And I'm actually an ex-officio member of the Scientific Advisory Board of SmartTots, and so what I'm telling you is what they're trying to do, and if anybody has any ideas about how to do that more effectively and get it done, more than happy to hear it. But it's a challenge because as you can imagine, sponsors are not that interested in funding studies that would show that their drug actually creates neuroaptoptosis. Until someone has something that would be a treatment, that's not going to happen.

So that's part of the ambiguity. Yeah, more work needs to be done on this, but whether or

not safety monitoring in a passive event reporting system is going to give you what you want is the question. And if you can come up with a recommendation, certainly happy to think about how that might be, how that might be executed beyond everything that's going on within the Division to try and answer this broader question of how -- I mean, the reason you're seeing this drug being used that often in my view is because people are thinking maybe this is safer relative to that, but that question has not actually been answered.

DR. HAUSMAN: Yeah, Ethan Hausman again. Just a small point of clarification on what Dr. Nelson said. The data entry into FAERS, the collection, that is passive. The monitoring that pharmacovigilence does, that's an active process. So routine surveillance does not mean that Dr. Pollock will now forget about this drug, and come back to it in five years, for example, if there were another labeling change that necessitated coming to the PAC of the OSE review. And I won't get into this too deeply, but the

Pharmacovigilence reviewers have drug portfolios that they monitor. Dr. Pollock may or may not have looked at this drug a couple of months ago just as a general matter of interest.

So going back to routine surveillance does not mean forgetting about a drug for a year or three. It means it goes back into the queue, and it comes back as it normally would in the reviewer's portfolio.

And I'll stop talking now and see if OSE wants to add on, or not.

DR. POLLOCK: Just two other comments about the cases for follow up. I want everyone to know that both of these are foreign. The first one is from Australia. The second is from France. That would make it more difficult. So the sponsors sent us these cases from those affiliates.

And this is my opinion. If we had that second case, all the records, it's highly confounded. The patient was very, very sick, and had lots of problems. The first one possibly

there's something going on, but I don't think the second one we could learn anything from.

DR. HUDAK: Okay. So we'll do Dr. Mink, and then Dr. Cnaan, and then Dr. Towbin.

DR. MINK: John Mink. I just wanted to completely endorse the comments of Dr. White. I think, yeah, the comments that were just made about the second death being someone who was very, very ill, it was also a 26-week premature infant. And, yes, it may be safer, but one of the things that I feel kind of frustrating about the role of this Committee is that I think we all recognize there's increasing use, and we are dependent on recording for safety, we really need organized trials, and I don't know how else other than to make publicly available comments to endorse that. But this is a common thing. A drug gets approved for use in adults. Someone says, well, maybe it's good in kids. We'll try it. We often do that. As a practicing physician, I use many things that are off label because they're not approved for use in children.

But I also try to be honest with myself that anecdote is not singular in scientific data, and I really think particularly for medications like that are using the sickest of the sick, we need data.

DR. CNAAN: Avital Cnaan. First of all I'm into that, but what I wanted to note is that in the data we received, there were maybe 100,000 prescriptions in the year right before the label changed that said, hey, there were three studies that did not work, that did not meet their efficacy.

What I wonder is whether we should see this back actually in a year, and see if anything at all happened after the label change, or if there's anything that the FDA can do about the fact that there was a label change given what you're all describing.

DR. NELSON: So I can guarantee you there will be no change in clinical practice based on those studies. You know, so -- and I won't comment since I didn't review the studies as to

whether the studies were quality or not, but, obviously, you know, more work needs to be done. So there will not be a decrease in use guaranteed, because what's driving this is not so much the drug itself, but the attempt to try and avoid these other medications.

And to give you context, I just pulled up the consensus statement which you can get from the smarttots.org which was updated in, I think, December of last year, or October of last year. I mean, it's signed by the American Head of Pediatrics, the Society for Pediatric Anesthesia, the FDA, the International Anesthesia Research. It's signed by the Canadians. It's signed by the New Zealand and Australians. It's signed -- I mean, everybody realizes there's a need here. It's even signed by the Wisconsin Society of Anesthesiologist, Peter, just out of deference.

Everybody realizes this needs to be done, so the issue here is getting the resources to do it. And I'm talking just the financial resources to conduct the clinical trial that would

answer this question.

You're welcome to ask for more use data, but I will guarantee you it will not go down over the next year based on that labeling change.

DR. TOWBIN: So I just wanted to make two comments. There's actually two ways in which there is off- label use of this. One is, of course, for the age group for which there's no indication, and that's very clearly stated. The other is the duration of the use. The drug is not approved for longer than 24 hours, yet most of the cases that I saw had much longer than 24 hours of use.

And so I guess that leads me to a request as we go forward with these efforts to shape data, SmartTots, and so on, that both of those things would be looked at. I find it remarkable.

DR. HUDAK: Skip.

DR. NELSON: Skip Nelson again, and if I can comment. We are acutely aware, I mean, certainly as a Boarded, but former, I guess,

pediatric critical care physician, that these medications, one started in whether it's the NICU or the PICU, are on for days and days and days.

Figuring out how you design that trial is even more difficult than figuring out how you design the trial for the kids that are maybe getting a three, or four, or five-hour surgical procedure.

So it definitely is an area that people are aware of. I raise it as a concern from the standpoint not only of this drug, but a fact that while you're intubated and ventilated, you are receiving medications that are known to produce neuroaptoptosis. So it is a big issue, and it's -- without being totally inflammatory -- well, I'll say it. I mean, I sometimes say if this signal is real, this is like lead in our, you know, I mean -- now granted a lot of these issues are confounded. Kids are sick. They're in the hospital a lot. But this is a question in my mind that needs to be answered, and it's just a question of getting the financial traction. I

mean, the anesthesiologists are motivated to do this in the international scale. It's just the question of getting the resources to do it.

And that's a challenge, and FDA can't do that. We're helping fund this public/private partnership, but ours is just a little bit of seed money to figure out a way to get more.

DR. TOWBIN: Well, this is Kenneth again. Of course, not to question the FDA's interest, passion, or motivation to participate in that process, but as a member of the Committee, and to kind of voice the sentiments of the Committee clearly, we certainly stand with you. We are concerned about this.

You talked about lead. It kind of reminded me of using 100 percent oxygen. It's just one of those things where we wish we had the data to avert future consequences. So thank you.

DR. HUDAK: Dr. Davis.

DR. DAVIS: One of the things as you described the death from the preterm infant was the fact that the serum levels were three times

what, if we really know what the normal range is for this drug, and I'm not sure we do, but whether or not in your vigilance if we're -- because you have the opportunity to look at these drug/drug interactions which is probably more problematic that there was also two other drugs, Sufentanyl and Levopromazine, and whether there was inactions with all three, you also had a critically ill baby, and whether or not there are opportunities to look at the recommended dosing that may be published and issue guidance or advisory that if there is a critically ill child that there's -- that maybe some of those doses aren't necessarily accurate or may be too high and associated with other complications. I know based on one case, it's difficult to do that, but whether or not your monitoring might allow you to do that with more data as it comes in.

DR. HUDAK: So I'll finish up, I guess. I have two comments and a question. The first is, I agree with Dr. Hoehn's concern about what dose was used in this ten-year old child with Rett's.

If this had occurred at any one of our hospitals, we would have done a thorough investigation given the circumstances, and my primary concern would have been whether or not there was a massive overdoses of medication that was inadvertently administered.

My second comment is that I agree with everybody else. We are seeing these drugs used more and more frequently in the critical care setting. My experience in the PICU is patients on ECMO, who get started on this drug sometimes concurrently with fentanyl versed when those drugs -- patients become tolerant of those drugs, occasionally attempt is made to wean the patients off fentanyl, but that's really not the primary rationale.

And similarly, in the NICU, I think use is expanding. There had been a series of case reports have been published looking at this drug in pre-term babies, and I think neonatologists just in general have interpreted these reports as supportive of use in that setting even though I

don't we have good information.

The question I have is that in your reporting on this, there were a number of adverse events which -- had not been identified on the label. I think syncope and torsades and others, and the question is at what point during routine monitoring do you accumulate enough of these reports on these different adverse events do you consider adding it to the label?

DR. TAYLOR: It varies it would be a matter of looking at the cases to see what was involved. Whether there were any confounders. You know, was this a compelling case. And then I don't know that there's a set number that we say we must have a certain number, and then we would consider labeling it.

I don't know if the Division has anything else they want to add?

DR. ROCA: This is Dr. Roca. I agree with you, and part of it is going to be the quality of what you're seeing because, obviously if you have one case, and you've got all the

information you need to really be able to make a strong conclusion that you think it is related to this case, you're probably going to do something about it as opposed to having five cases where you have information and you really can't put your arms around it. So a lot of it depends on the quality.

DR. HUDAK: Dr. Nelson.

DR. NELSON: So let me make a suggestion, and I'm not sure what the timing of this is. I mean, there's been a lot of discussion on this. For example, if -- and we can send the link to the Committee members if they're interested. There was a Science Advisory Board meeting now about a year and a half ago where some of the preclinical data were presented by a absolute tour de force by Merle Paul, who is at the National Center for Toxicology Research of FDA, around all of the preclinical data all the way from nematodes up to nonhuman primates, all consistent.

So it's unclear to me when -- I mean

StartTots is active -- whether or not -- at the GAS study there's five studies that are ongoing. You can look. You know, whether in two years. It's hard to know when there'd be some more clarity, but, certainly, if the Committee wanted to make a recommendation recognizing the limits of the adverse event reporting system.

And as Ethan said, I mean, we look at it whether or not you'd see anything different because the use going up or not, but if I was going to look at this again, I would try to sort of set it into a broader context than simply the use of this drug. So, I mean, that's, you know, I'm not sure. SmartTots has been struggling. It's hard for me to know when there'll be any clarity, but, certainly, a conversation at some point two or three years from now about the broader issues could be, perhaps, anticipated. But I even -- I mean, it's hard to know when we'd have information.

Again, there are studies being done under IND, but who's doing them and what, we're

not supposed to tell you because it's illegal. So I don't know, Rigo, if you have any sense of that. Because the problem is taking this drug in isolation apart from the broader issues that are raising I think is part of the problem.

DR. ROCA: I totally agree. I think it is important to take a look at broad scope, and I'm glad you mentioned the Science Board meeting we had. And I think bringing the weight of this Committee to the issue would also help. I think having the Pediatric Advisory Committee lend their support for the need for additional studies would be important, would be useful.

As far as when we would bring it back that was your question of the timeline. That is hard right now just as to when would be a good time when we would have additional data for you. I do note that, as you mentioned, there's some non- clinical information still -- even with respect to dexmedetomidine there are some preliminary results out there that not necessarily presenting an abstract but preliminary, but

something in the abstract that they do have some changes in other parts of the brain compared to ketamine.

What does that mean? What clinical implications we have, we do not know. But there are -- there are things that's saying maybe we don't know everything that we think we know. So that's one thing.

And with respect to the GAS study, yes, they did publish, I believe -- presented, at the very least -- the preliminary study, the preliminary results. They still need to have a follow up to two years. So the preliminary results didn't show any difference, but we're still waiting for the final assessment.

So we're still up in the air. Actually, that might not be a bad timeline. When GAS finishes, do you think that that might be worthwhile coming back after GAS?

DR. NELSON: If I had to guess, I would say two to three years would be the hope. Earlier than that there might -- I mean, if it all comes

in. So, I mean, I, you know, if you're agreeable I'm fine. I know that I always hesitate. The Anesthesia Division is at this point drowning in advisory committee meetings because of the opioid issue, but something two or three years from now you always promise, and I think that would be fine.

Now that's a -- whether we get anything -- I mean, at that point, we could, certainly, update the safety monitoring, but I suspect there be more information that would get from some of these other activities. Maybe there would be some from the safety monitoring, but we could do that at the same time.

So I guess that would not be routine. And if the Committee wanted to formulate that as a recommendation, certainly, that would be reasonable.

DR. ROCA: And we'd be happy to come back and --

DR. NELSON: Right.

DR. ROCA: -- update the Committee on

whatever information we may happen to have at that time.

DR. NELSON: So that would be about the timeline, I could imagine, that would be useful. And if the information is early, it's not like we would wait, but it's just to do it prematurely when you don't have stuff on the table might not be that easy.

DR. HUDAK: I think Dr. Towbin had his hand up first. I'm going to ask him maybe make a recommendation for a motion.

DR. TOWBIN: Yes. Well, actually, two things. So I just had one quick question. The data that were given is exclusively pediatric data. I, looking at these, wonder if there was any such signal for similar unlabeled events in any of the adult reporting.

DR. POLLOCK: This particular review is just on pediatric. It's not meant to address any adult data.

DR. TOWBIN: So we wouldn't know -- this is Kenneth Towbin again. We wouldn't know if

there were events like Syncope, or some of these other cardiovascular events occurring in adults.

DR. POLLOCK: Yes, from this evidence, correct?

DR. CRISAFI: Many of the events that were observed in the Pediatric FAERS review are already in the labeling for adults, have been observed, and have come through, I think, FAERS data findings in adults.

DR. TOWBIN: Right. I think my question is -- Kenneth Towbin again. My question was specific to the unlabeled events that we saw on this pediatric data, and I was wondering if there were similar unlabeled events in the adult data that we might be able to know about.

DR. POLLOCK: We have not studied that in particular.

DR. TOWBIN: So that would be of interest, I think too -- this is Kenneth Towbin again. That would be of interest, I think, to some of us. So that being said, I think that I'd be happy to frame a proposal here.

So I would propose that we hear back as soon as possible when this study is done, the GAS study that you've referred to. And I think just to speak for myself but to echo what others have said, I think we are concerned about the large off-label use of this drug in the pediatric population, and for the duration of its use, and that we strongly and keenly support the FDA's efforts to obtain better, high quality data since the initial studies that were done really were so lacking.

DR. HUDAK: Dr. Hoehn.

DR. HOEHN: I had a follow up to that which was a question which was I didn't know if it was possible for the FDA to change the label to recommend reporting if there's adverse events in use over seven days. A few people mentioned that a lot of the problem is that it's passive reporting, and so I didn't know if there was anything to encourage people to report -- I know you can't do mandatory reporting, but if there's anything to say, hey, we're watching you. The FDA

is keeping an eye on this. If there's events you're seeing after seven days of use with high doses or over a certain dose, we would encourage you to report it. I know people already do that I know that they've done that, if there was any other way to encourage reporting for longer term use.

DR. ROCA: Well, I think we can certainly make that comment. I would suspect that sometimes we probably would have a little bit of reticence from people reporting an adverse event when they're using it when it's contrary to what the label supposedly is indicated for.

So I wouldn't be surprised if people would be a little bit reluctant to report an adverse event in that situation. But we can, certainly, encourage people to do that because it will, certainly, help fill out the database that we have.

DR. HUDAK: Yes.

DR. TURER: Christy Turer. So one of the questions that I have relates to what I study,

which is obesity. And that as I was reading through the studies not just for this drug, but for many of them, the way that we think about dosing, we think of it as per weight, or body surface area.

So I wonder in your safety monitoring if you do alternative weight indexing. So, for example, ideal body weight adjusted dosing. There is also an ideal body weight based body surface area adjustment that can be done. Same thing for glomerular filtration rate.

And this -- I wonder if it could be confounding some of these signals. And, certainly, overweight and obese kids are more likely to be hospitalized, to get very sick, to be in the ICU, and to receive some of these drugs some of which are lipophilic, not all.

DR. ROCA: This is Dr. Roca again. Is your question whether there is a way of trying to get at that information through the FAERS, or I'm not sure what your question is. Because I agreed with your points of observation, but I'm not quite

sure what the question is --

DR. TURER: So the question is do you do just weight-based adjusted dosing, or is there a measure to look at alternative ways of dosing, such as ideal body weight adjusted versus raw weight adjusted, and same for body surface area.

DR. ROCA: In general we do. And I don't think we have anybody from clinical pharmacology with us today, but, yes, we do, and a lot of it depends on what you yourself mention is there are properties of the product. If a product tends to be more lipophilic, then some of those factors will come into play more than in the product that wouldn't be affected by those kinds of things.

So we do look at that type of dosing as a part of this going through instructive Baumann phase.

DR. POLLOCK: In general, in many of the FAERS cases, we barely have weight, but I don't think I've ever much seen height if we would need to make a more extensive calculation that you're

referring to, the ideal. So I don't think we have the data in our cases to get that ideal body weight.

DR. HUDAK: Dr. Nelson.

DR. NELSON: I just thought it might be useful for me to summarize in my own mind what this meeting would look like in the two to three-year range just to make sure we're all on the same page.

So, first, you know, dexmedetomidine in terms of the review of adverse events would be part of that, and we, certainly, explore avenues for seeing if we can encourage reporting. There are avenues that are separate from labeling and the like to see if that's doable.

But the context for that would be placing what I assume will be a continued use, maybe even an increased use of dexmedetomidine and the use data into the context of the overall issue of neuroaptoptosis for particularly young children below two and three years of age surrounding inhalational anesthetics and

sedatives, and to time that when there are data that are available out of some of the studies that have been funded through SmartTots in little bits and pieces. The GAS study. There are some epidemiology studies to just see where are we at that point, and whether or not that conversation could fold into it issues around clinical trial design or not, I guess, would be open.

I would hope we would have sorted out a trial design by then, but it's still an ongoing discussion. And as part of that, also, frame it within the context of the ongoing preclinical data, but particularly whether there's preclinical data on dexmedetomidine that's evolved at that point, which at this point has not been the main focus of the non-clinical studies that have been done.

Now, so that's what I would imagine that meeting would be. Now granted, so that kind of meeting that's going to be probably a full day, I mean, or at least half a day. I mean, it would take time do that. The Science Board I think was

at least half a day on this topic. And I think the PAC likes to have more topics.

Now, having said that, I don't think the -- the FAERS data will be part of it, but I don't think it's the major driver. But what I would suggest then when you're looking at this question with the understanding that that's what such a vote means is that meeting, you're voting no on routine monitoring. I mean, that's -- and what I'm suggesting to you is my interpretation of a no vote is what I just said relative to a commitment to do a hard look at this issue within a broader context in the two to three-year time frame. So that's what a, in my mind, a no vote would mean on this. Okay. It doesn't necessarily, you know, I mean, but the FAERS part is a small part of that overall commitment. So just to clarify what that would be.

DR. HUDAK: Wow. So I'm going to maybe recast that discussion.

MR. NELSON: I know you don't normally vote no when we ask you to concur, but I just

wanted to say if you do, that's how I interpret it. So --

DR. HUDAK: Well, I think, I think --

DR. NELSON: If you vote yes --

DR. HUDAK: I think that we want to be sure that the activities that are ongoing continue. And in addition, I think the sense of the Committee is that we agree with you that a more robust discussion of this in the context of more global issues is indicated.

DR. NELSON: Right. But that's not routine post-marketing monitoring. We're still going to do what Ethan said we do actively. I'm not saying we just, we stop doing that. But the point is, this is above routine monitoring.

Now, in the course of setting up this meeting, the FAERS part will be a part of, but not a big part of, because this broader context needs to evolve. So I just wanted to -- sometimes there's confusion about whether you vote yes for a meeting, and then no or yes for this. I'm just trying to clarify that if this is what you want,

it's a no vote on this question. And that will mean if you want to then vote yes on the meeting separately, I'm fine too. But this is not routine monitoring that you're voting for.

DR. HUDAK: Dr. Towbin.

DR. TOWBIN: Well, seems to me that we need two votes. One is for the request for this meeting as you've outlined it so nicely, Dr. Nelson. And then a second vote related to whether we concur with -- I think that it would be too ambiguous to kind of fold them all into one.

It seems to me from what you just said that the monitoring would go on anyway so we don't need to vote for that. It's the routine part that becomes the question mark. And so I would like to propose that we have a vote on the issue of a meeting to review the data, as you've described it, and discuss the plans for the subsequent research to learn more about this drug and its effects.

DR. HUDAK: Dr. White, did you have anything to add?

DR. WHITE: Michael White. I second what he just said. That would be an excellent way to approach this.

DR. HUDAK: Okay. We will call a question, and could you restate your motion in a sentence or two, Dr. Towbin?

DR. TOWBIN: You do raise the bar very high. I propose that the FDA come back to us as soon as it can with the information from the GAS studies, a review of adverse events and use at that time for -- and the plans for the prospective research, the data, if you will, plan for this particular drug, and that we would hear about it back here at the Pediatric Advisory Committee at that time.

DR. HUDAK: Okay. So we will call that recommendation into vote. Open up the blinking green lights.

(Pause)

DR. HOEHN: Just to clarify again, we're voting only about the second meeting dedicated to dexmedetomidine, yes?

DR. HUDAK: That's correct.

(Pause).

DR. HUDAK: Okay. So we have a unanimous recommendation to resolve to the FDA for an additional meeting and information around this product in a context of other issues so very well stated by Dr. Towbin. So go around the room.

DR. WALKER-HARDING: Leslie Walker-Harding. I concur.

DR. TURER: Christine Turer. I concur.

DR. BAKER: Susan Baker. I concur.

DR. KASKEL: Rick Kaskel. I concur.

DR. MINK: John Mink. And solidly -- concurrence.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. WHITE: Wrong button. Michael White. I agree.

DR. CELENTO: Amy Celento. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. RAKOWSKI: Alex Rakowski. I concur.

DR. TOWBIN: Kenneth Towbin. I concur with my thanks to everyone.

DR. DAVIS: John Davis. Concur.

DR. MOON: Marc Moon. Concur.

DR. DRAKER: Bob Draker. I concur with just one comment. I think when certain drugs come along with significant clinical usefulness in pediatric populations, I think somehow as Dr. Towbin suggested there should be a recommendation that we need more clinical data, or strongly encourage a clinical study to see how a drug can be used on label rather than off label for pediatric populations that we're concerned with.

DR. CNAAN: Avital Cnaan. I concur with the one additional request that Dr. Towbin expressed earlier, which is in that meeting to see the unlabeled events in the adult population reported as possible.

DR. HUDAK: Okay. So we -- that is a

completely separate motion, I think. So I don't know that the Committee needs to vote on that, but I think it is the sense of the Committee that looking at the adult information to see if there's a similar pattern of unlabeled events might be useful.

And then I guess we need to turn to the -- if we go back to slide, we need to deal with the semantical question here of what to do with this vote on routine monitoring.

So the question is does the Committee concur with the recommendation to continue routine -- I'm going to take the license and say that we will vote on the proposition that the FDA continue it's current procedures which are routine, but are not restricted to be routine because we have voted on additional -- I just don't want to get a motion that's going to be confusing.

So the motion is that the FDA would continue their current procedures and monitoring on this drug to be supplemented, obviously, by additional information be brought forward. Is

that clear?

DR. HAUSMAN: Yes.

DR. HUDAK: So we'll do the vote, we'll do the blinking green lights.

(Pause)

DR. HUDAK: And we'll go around the room starting with Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRAKER: Bob Draker. I concur.

DR. MOON: Marc Moon. I concur.

DR. DAVIS: John Davis. I concur.

DR. TOWBIN: Kenneth Towbin. I concur with ongoing monitoring.

DR. RAKOWSKY: Alex Rakowsky Concur.

DR. HAVENS: Peter Havens. Concur.

DR. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White. Concur.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. HOEHN: Sarah Hoehn. Concur with ongoing monitoring. Continue to encourage more reporting.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. MINK: John Mink. Concur.

DR. KASKEL: Rick Kaskel. Concur.

DR. BAKER: Susan Baker. Concur.

DR. TURER: Christy Turer. Concur.

DR. WALKER-HARDING: Leslie Walker-Harding. I concur with current ongoing monitoring.

DR. HUDAK: Very good. So the recommendations are to continue current monitoring, and the second recommendation to expand data acquisition analysis on this product in the context of other products at a future meeting as soon as possible.

And, Dr. Taylor, you're running a marathon here. You now offer your third consecutive presentation.

(Pause)

DR. HUDAK: And while we're at a pause here awaiting other members to arrive, if you can introduce yourselves once you get seated.

DR.. KORVICK: Joyce Korvick, Deputy Director of the Division of Gastroenterology and Inborne Errors Products.

DR. SWANK: Kimberly Swank, Safety Evaluator, Division of Pharmacoviligance.

DR. GREEN: Patty Green, Drug Use Analyst.

DR. TAYLOR: Thank you. I will be presenting the Pediatric Focused Safety Review for Aciphex Sprinkle, or rabeprazole. This is an outline of my presentation.

Aciphex Sprinkle was originally approved on March 26th, 2013. Aciphex is also available as a delayed-release tablet, which was approved for marketing on August 19th, 1999.

In the next few slides, I will present general information in labeling which is relevant to both pediatric and adult patients. That will be followed by a brief discussion of new pediatric information.

Aciphex is approved in pediatric patients for short-term treatment of symptomatic

GERD in adolescence aged 12 years and older, and for the treatment of GERD in patients one to 11 years of age.

This slide lists the contraindications in labeling, and some of the warnings and precautions.

This slide lists the additional warnings and warnings precautions.

The next two sides will discuss the pediatric studies supporting the approval of Aciphex Sprinkle. In pediatric patients 1 to 11 years with GERD, a randomized double-blind clinical trial was conducted. 81 percent of patients demonstrated healing after 12 weeks. 90 percent retained healing after 36 weeks.

In pediatric patients one to 11 months with GERD, a randomized placebo control withdrawal trial was conducted. The study did not demonstrate efficacy based on an assessment of frequency of regurgitation and decreased weight for age Z-score. These results will be expected since GERD in infants is not acid mediated.

I will now focus on the labeling changes. An indication for treatment of GERD in patients 1 to 11 years was included in Section 1. Dosing recommendations were included in Section 2, and the adverse reactions section was updated with new safety information.

Section 8.4, Pediatric Use, included a description of the completed studies as well as a statement that use of Aciphex Sprinkle is strongly discouraged for the treatment of GERD in neonates.

Section 12 includes pharmacokinetic information, and Section 14 includes information about positive studies.

I will now discuss drug use trends. There were 3,486 patients with a dispensed prescription for Aciphex Sprinkle from outpatient retail pharmacies for the review period. Pediatric patients are 0 to 16 years accounted for 89 percent, or approximately 3,100 patients, while patients age 17 years and older accounted for approximately 11 percent of total patients. Pediatrics was the top prescribing specialty with

approximately 46 percent of patients for Aciphex Sprinkle, followed by gastroenterology with 14 percent of patients. Esophageal disorder not elsewhere classified was the only diagnosis reported among pediatric patients age 0 to 11 years.

I will now review the FAERS case series. There were 14 total pediatric reports all of which were recorded as serious. There were no deaths. All 14 reports were reviewed. Five reports were excluded for the reasons you see here. This left us with a case series of nine pediatric cases.

This slide presents the demographics and characteristics of the pediatric case series. There were four cases with a serious, unlabeled adverse event: Headache, vertigo, and blurred vision. Of note, vertigo and blurred vision are labeled events for other PPIs. There was one cases with lymphadenitis. One case with increased Beta 2 microgloblin and hematoma. There were five serious labeled adverse events: An upper limb fracture, viral infection, bronchiolitis, and

dehydration. Also, bronchopneumonia, intentional overdose, and renal impairment.

Of note, in September, 2015, FDA reported a potential signal of a risk of systemic lupus erythematosis and proton pump inhibitors. FDA is evaluation the need for regulatory action.

This concludes the Pediatric Focused Safety Review of FAERS reports. Potential safety signals of vertigo, and blurred vision were identified. FDA recommends adding vertigo and blurred vision to prescribing information for all dosage forms of Aciphex.

Does the Committee concur? And I'd like to thank these folks for helping me with this presentation.

DR. HUDAK: Okay. This is open for discussion. Thank you, Dr. Taylor. And Dr. Rakowsky.

DR. RAKOWSKY: Thank you, Dr. Taylor.

DR. HUDAK: Oh, okay, I'm sorry. We have another person who has joined the table? He's in my peripheral vision. Could you introduce

yourself? Thanks.

DR. LEVIN: Hi. I'm Bob Levin from the FDA, Director of the Division of Pharmacovigilence 1.

DR. HUDAK: Okay. Dr. Rakowsky.

DR. RAKOWSKY: So regarding the blurred vision and the vertigo case, that child got a four to eight times higher dose, so would that change be just because all the other PPIs have it in it so it's like a class label change, or is it really because of -- wouldn't there be more overdose information?

DR. TAYLOR: I think your answer, yes.

DR. RAKOWSKI: For the class label?

DR. TAYLOR: Yeah. I mean, because it's in other labels, and so we now have a reported case. I mean, it, you know, it is potentially an overdose, but this occurred, so it gives us an opportunity to add this to Section 6, Post-Marketing Adverse Events.

DR. HUDAK: Dr. Havens.

DR. HAVENS: In the utilization

information available to FDA, is there any information available on the duration of use of these drugs? I ask that question because it's relevant to the issue of growing bones and the effect on bone, or effect on bone of this class of drugs, and it would be a useful, perhaps useful bit of data to include going forward.

DR. KORVICK: For our current analysis, we did not include a duration of use analysis. It's not something that we do standard for this review, but it is something that we potentially can provide in the future.

DR. GREENE: You should know that the Division is looking into reports in pediatrics. There was a post-marketing adverse -- a post-marketing safety PMR with Dexilant, another drug in this class that is coming in. You know, these studies are listed at the website, you know, nichd.gov, you know, for clinical trials. But anyway so we'll have some data there, and they're also more interest in across the class looking at animal, more animal data, and really understanding

what this all means within the class for bones and for other adverse events that might take, you know, a year or two of continuous use to sort out. So we are actively looking at those kind of things in other ways besides FAERS.

DR. HAVENS: The label has it for adolescent patients 12 years of age and older, it's indicated for short-term use, and in pediatric patients 1 to 11, there's no time limit noted in the labeling, I think. It just says treatment of GERD. And does that imply short-term use or is the duration of use --

DR. KORVICK: So we usually try to put that in the labels, so I don't know if you're referring to -- this isn't a representation of the label, so I don't have the label in front of me. And is that the one that we just approved? So, you know, we usually put this under -- so is the -- so, okay. So this was very confusing, and I don't know what label you had, but in the -- we are working on clarifying that and updating the label for Sprinkle to very specifically say, you

know, the durations. We usually like to do that. So if that's an oversight in the current label, it might be clarified in a future version.

DR. HAVENS: Thank you.

DR. HUDAK: Dr. White.

DR. WHITE: Michael White. Looking at the data, percent of the use of Aciphex Sprinkle was under one year of age, and there's no labeling for it under one year of age. Is there any way we could request the company to get some data of pediatric request or otherwise?

DR. KORVICK: So we have a lot of these different requests and so forth that were written over the years, and this is not unsimilar to what we've done for the other PPIs, and I think if the efficacy data was not -- I think you have a slide here that talks about the data. One to 11 months do not support.

I don't know if the sponsor is conducting a study in that age group at the current time. There are some outstanding PMRs, PREA PMRs, but my colleagues would have to look

that up for you.

DR. HUDAK: Dr. Nelson.

DR. NELSON: Just as a reminder, there was an Advisory Committee that was conducted maybe two-ish, or three-ish years ago that basically of the G.I. Committee. I don't recall if there were any members of the current committee at that meeting, but basically GERD below a year of age is not an acid-driven disease. Acid suppressions doesn't do a thing for it. And so there are no studies at this point that really you would need. And so bottom line is this is being used by people that people that haven't read the fact that there is no clinical indication for this below a year of age. And that was pretty much the firm conclusion of that Advisory Committee meeting.

So there's not a need for studies here. There's need of education for the fact that it's not effective in -- it's, in fact, not even a treatment of a disease that exists in someone who is a month, or, two, or three years of age.

DR. WHITE: Michael White.

DR. KORVICK: I think what -- I think what you asked was the adolescent group. Is that what you --

DR. WHITE: No. Less than one year of age.

DR. KORVICK: Well, the --

DR. WHITE: So is there --

DR. KORVICK: -- it's indicated for one to 11 year of age in a study less than one year failed.

DR. NELSON: It's not considered a disease that responds to acid suppression at less than a year of age.

DR. WHITE: So is there a way to put it in the label to get people to say it doesn't work and it's not --

DR. KORVICK: So we've --

DR. WHITE: I guess it's already -- okay.

DR. KORVICK: So we've put that in the label in the way that we're supposed to put it based on all of our guidances of labeling and how

we say this. And you're right. This, you know, this has been a problem for many, many years. So education I think is, as Skip said --

DR. HUDAK: It's in the label. That is strong discouraged. So Dr. Kaskel.

DR. KASKEL: There's a recent report in the literature in JAMA last month about the increasing sense of chronic kidney disease in adults without kidney injury taking PPI for prolonged periods. So there's signal here, I think we have to be cognizant of especially in the children. Okay. So an area to look at.

DR. KORVICK: I just have to let you know that everyday there is another epidemiologic observational study in PPIs in general that report a safety event. And we are monitoring those, and we are doing reviews of those issues, and I think that this current FAERS review didn't reveal those cases, but as we are exploring those issues that we will consider that.

DR. WHITE: Great. Thank you.

DR. HUDAK: Dr. Towbin.

DR. TOWBIN: Well, I'm intrigued by this comment about lupus associated with this drug. And I'm just curious about where things stand. What the plan is for learning more about that, if I heard correctly.

DR. KORVICK: So we are -- we have a review that's underway, and usually what results from those reviews as the colleague earlier said, there's a track safety issue for this. This is a review of cases of drug associated lupus, you know. So probably any drug could do that if we sat here and looked for that. But PPIs everyday in every way they have another observational something study that plays big in the press.

So, you know, we are actually scrutinizing the cases that have been reported to us, looking at the literature, and usually then what results from that is a change in the label. So, you know, I can't say right now today what those actions will be, but I anticipate that you'll know about this as we uncover these cases and do a thorough review.

DR. TOWBIN: Thank you.

DR. HUDAK: And I guess I would be remiss as a neonatologist not to comment on the fact that although there is nothing in the presentation that speaks to children less than one month, these agents came out. They were immediately adopted for us in the NICU, but thanks to a recently published study on choosing wisely, in the NICU this is one of the issues that was strongly discouraged because of lack of data, and potential adverse effects in other systems. So --

DR. KORVICK: I've been -- in follow up to that, I think you know the agency after several of these advisory committees also published a paper after we got the result of those studies to give the data to the groups at large. So I am very happy to hear that there are other groups that are continuing to send that message out. So that's very hopeful to me, and then maybe people will use this less in groups that it's not effective for. And, again, this is only effective for acid mediated events. And so thank you for,

you know, the outside group also reverberating that message.

DR. HUDAK: Any other questions or comments?

(No response).

DR. HUDAK: So we come to the question. And that is that the FDA does recommend adding vertigo and blurred vision to the prescribing information for all dosage forms of Aciphex, and this is going to go into the warning and precautions, or adverse events section of the label?

DR. KORVICK: Most likely will go where it is in all the other labels, and that right now is in Section 6.2, Post-Marketing Adverse Events.

DR. HUDAK: Okay. Very good. So we will open up for voting with a yes vote to agree with that recommendation.

(Pause)

DR. HUDAK: Okay. We will for the record go around the room. I think Dr. Walker-Harding, we'll start with you.

DR. WALKER-HARDING: Leslie Walker-Harding. Concur.

DR. TURER: Christy Turer. Concur.

DR. BAKER: Susan Baker. Concur.

DR. KASKEL: Rick Kaskel. Concur.

DR. MINK: John Mink. Concur.

DR. CUNNINGHAM: Melody Cunningham. Concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. CAMPBELL: Jeffrey Campbell. Concur.

DR. WHITE: Michael White. Concur. And I would like to request that the FDA find some way to educate that the use of these drugs under 1 year of age is contraindicated.

DR. CELENTO: Amy Celento. Concur.

DR. HAVENS: Peter Havens. Concur.

DR. RAKOWSKY: Alex Rakowsky. Concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. DAVIS: Jon Davis. Concur.

DR. MOON: Marc Moon. I concur.

DR. DRAKER: Bob Draker. Concur.

DR. CNAAN: Avital Cnaan. Concur.

DR. HUDAK: Okay, Dr. Taylor, thank you for an extraordinary dedication and endurance there in the hot seat. And we are now ready for excitement to go pick up our culinary masterpiece lunches, and regroup here for probably 12:35 by the time we get through the line and pay the bills, for a working lunch.

(Recess)

DR. HUDAK: Someone needs to blunt the music. Where's our AV folk. Okay, we need to turn the music off. Great. Thank you very much. Okay. So we will get started. It's still going.

SPEAKER: Got it.

DR. HUDAK: Okay. All right. So Dr. Quinto is back, and he is going during our lunch period to talk to us about a proposal for risk-based assessment which, hopefully will streamline the Committee's work in the future to concentrate only on those drugs that really need the intense consideration and review by the

Committee. Dr. Quinto.

DR. QUINTO: Good afternoon. Again, I'm Lt. Commander Ken Quinto, a medical officer in the Office of Pediatric Therapeutics, and I will be presenting the Risk-Based Assessment Proposal for CDER products.

This presentation has two objectives: Number one, I will describe the Risk-Based Assessment Proposal for the Center of Drug Evaluation and Research, CDER products for the members of the Pediatric Advisory Committee; number two, I will solicit feedback from PAC members about the Risk-Based Assessment Proposal for CDER products.

This is the presentation outline. I will start with a brief overview of the Risk-Based Assessment Proposal process. Then I will compare the proposed process to the current process, and discuss similarities and differences between the two. Lastly, I will discuss the advantages of the Risk-Based Assessment Proposal.

Let's start with a brief overview of the

Risk-Based Assessment Proposal process. In its essence, the Risk-Based Assessment Proposal is a modification to PAC review for certain CDER products that are designated low safety risks. The factors to determine low safety risk CDER products were built from existing criteria currently used to determine abbreviated presentations to the PAC.

The timeline for the Risk-Based Assessment Proposal is similar to the current review timeline, as you will see later on in the presentation. After the data collection phase, or the FDA Adverse Events Reporting System, FAERS, collects adverse event reports, meeting number one takes place. Day meeting number one, members from the Office of Pediatric Therapeutics, OPT, Division of Pediatric and Maternal Health. DPMH, Office of Surveillance and Epidemiology, OSE, and appropriate CDER division represent the review team. In this meeting, several issues are discussed including any upcoming product label changes and safety issues. The Post-marketing

Pharmacovigilence Review Plan, which includes corrected counts of FAERS cases to be reviewed, as well as the discussion of the Analysis Plan for Drug Utilization Data.

Prior to meeting number two, the Pediatric Post-Marketing Pharmacoviligance and Drug Utilization Review Draft, which is a draft of the final safety report including in your briefing materials is circulated. The review team discusses the reviews of the FAERS cases and the result of the Drug Utilization Data Analysis. Near the conclusion of meeting number two, the review team will decide whether product is low safety risk or not.

This flow chart shows the two different pathways available after meeting number two for the Risk-Based Assessment Proposal. If a product is designated a low safety risk product, it follows a process noted in green in the top portion of the slide. If the product is not designated as a low safety risk product, it follows a process noted in red in the bottom

portion of the slide.

The risk-based process will occur continuously throughout the year. Therefore, CDER products deemed low safety risks will be put on the FDA website throughout the year as well.

During meeting number two, the review team will consider the following factors in determining whether to designate the product low safety risk.

Number one. No pediatric deaths, or pediatric death likely attributable to disease progression. Number two. No or few serious adverse events, SAEs, attributable to the product. Number three. No new safety signals identified by the FDA through a later literature review, FAERS case review, drug utilization data review, and ongoing track safety issues for product or class of products. Number four. Product is adequately labeled for pediatric use, including dosing information and adverse events included on the product label. Number five. There is little pediatric or the number events relative to use is

not concern. As pointed out previously, the factor is to determine low safety risk CDER products were built from existing criteria currently used to determine abbreviated presentations of the PAC, as I will explain later on.

If at that meeting number two, the review team designated the product as low safety risk, reported edit phase begins in which edits to the safety report are made and the document is cleared. After clearance, the safety review report will be publicly posted on the FDA website for review. An open docket would be established for commenting.

When the Federal Register notice is published for the PAC meeting, we envision the notice including a list of products whose review reports have been posted to the FDA websites since the last PAC review.

Now back to the flow chart. If the product is not designated as a low safety risk product, it follows a process noted in red in the

bottom portion of the slide. If the review team does not designate the product as low safety risk, the review team must select a future PAC meeting to present the product. The product will then follow the same process as the current process including a rehearsal meeting, and eventual presentation to the PAC.

Now I will compare the Risk-Based Assessment Proposal to the current review process, and point out important similarities and differences.

This is an overview of the current process timeline to bring a CDER product to PAC for safety review. I'd like to bring your attention to meeting number two highlighted by the orange box.

Just like in meeting number two for the proposed Risk-Based assessment, the review team discusses the FAERS cases, the results of the -- and the results of the Drug Utilization Data Analysis.

Near the conclusion of this meeting for

the current process, the review team decides the presentation format either abbreviated or standard for the product. I'd like to point out that all CDER products reviewed by the PAC receive a full review. However, presentation formats, either abbreviated or standard to the PAC differ.

This diagram was presented to the PAC on April 12th, 2014 explaining the difference between the types of abbreviated presentation to the -- different abbreviated presentation which the PAC agreed to. The left portion of the diagram explain the factors used to determine the justified abbreviated presentation, and the right portion of the diagram explain the factors used to determine the abbreviated presentation, and the designated abbreviated presentation. Since the diagram is difficult to read, I will elaborate on the current abbreviated presentation factors further on the next slide.

In order for CDER products to be considered for justified abbreviated presentation formats, criteria one and two are considered,

including, number one, whether the product is used to treat serious and life-threatening diseases, and, number two, the deaths and SAEs are labeled appropriately and attributable to a disease.

In order for CDER products to be considered for the abbreviated presentation format, criteria three, four, and five are considered, including three, whether the product is used to treat non-serious or non life-threatening condition, number four, there are no newly identified safety signals, number five, the product is adequately labeled for pediatrics.

In order to be considered for the designated abbreviated presentation, the review team considers factors three through seven, which also include number six, no or few pediatric-related deaths or SAEs attributable to the product, and number seven, low, less than or equal to one percent for use in children, or not marketed.

Again, these are the factors to be considered by the review team to determine where

the CDER product is a low safety risk. These factors were built from criteria presented in the previous slide.

You'll notice that the same areas of concern are addressed, including pediatric deaths, serious adverse events, identification of new safety signals, drug utilization in pediatrics, and appropriate pediatric product labeling.

I will now discuss the main difference between the current review process, and the Risk-Based Assessment Proposal. The move from abbreviated presentations during PAC safety meetings to safety reports being on the FDA website.

Again, this is the flow chart that shows the two different pathways available after meeting number two in the Risk-Based Assessment Proposal. If the product is designated as a low safety risk product, it follows a process noted in green in the top portion of the slide. To emphasize, once a product is designated as a low safety risk, the Pediatric Post-Marketing Pharmacovigilence and

Drug Utilization Report is edited, cleared, and posted on the FDA website for review. An open docket will be established for commenting. If the product is not designated as a low safety risk product, it follows a process noted in red in the bottom portion of the slide.

In the current review process, all CDER products follow the process noted in red, and differ only in presentation format, either standard or abbreviated.

I will now present the advantages of the RiskBased Assessment Proposal. The advantages of the Risk-Based Assessment System include more time for the PAC to discuss CDER products that are not designated low safety risks at the meetings. Safety reports of products designated low safety risks will be posted to the FDA website for review and comment, and no longer will be presented at the PAC safety meetings, thereby allowing more time for discussion of CDER products presented to the PAC.

Since adaptation of the current PAC

presentation format from 2012 to 2015, 99 CDER products were reviewed by the PAC with 46 products reviewed in standard presentation format, and 53 products in abbreviated presentation format. Approximately 53 percent of CDER products reviewed by the PAC were presented in an abbreviated format.

The abbreviated presentation process was meant to more effectively use the PACs time. However, even with the current process in place, there's a backlog of CDER products awaiting PAC review.

With implementation of the proposed Risk-Based Assessment, we envision more time for discussion of CDER products presented for the PAC safety review at the PAC safety meeting.

Based on data collected from the PAC safety meetings, an OPT safety database from 2012 to 2015, an average of 22 CDER products were reviewed by the PAC per year with a range of 19 to 24. An average of 34 CDER products become eligible for PAC review per year with a range of

29 to 39 resulting in a backlog of CDER products awaiting safety review, which brings me to the next advantage of the Risk-Based Assessment Proposal.

An additional advantage to the potential -- an additional advantage is a potential to decrease the backlog of CDER products awaiting PAC review over time. In the future, we envision using continuous quality improvement, CQI process, to further increase efficiency and potentially the number of products the PAC reviews each year.

As such, we anticipate forming an internal, multidisciplinary steering committee that meets once to two times per year to further improve and make efficiency gains in the review process. In the future, we also anticipate soliciting PAC comments on the CQI process as we move forward.

As of December 31st, 2015, 37 CDER products await PAC review with a median waiting time of 26 months. By December 31st, 2016, an additional 44 CEDR products are eligible for PAC

review. Using the 37 products currently awaiting PAC review, the 44 products that will be added to the backlog by the end of 2016, and the 12 additional CDER products added to the backlog each year after that, we have projected the number of CDER products in the backlog increases almost 300 percent from 2015 to 2020 using the current review process. As illustrated with the protected backlog of CDER products awaiting PAC review, we hope to further improve on the efficiency and effectiveness of the pediatric focus safety reviews using a Risk-Based Assessment process.

Through the implementation of the Risk-Based Assessment Proposal, we aspire to, number one, decrease the number of CDER product presentations during PAC pediatric focused safety meetings. Number two, as a result, increase discussion time of CDER products presented during PAC safety meetings. Number three, find further affinity in Risk-Based Assessment process through continuous quality improvement. And number four, as further efficiencies are identified, hopefully

increase the number of CDER products reviewed per year.

This is the end of the presentation. Thank you for your attention.

DR. HUDAK: Thank you, Dr. Quinto.

DR. NELSON: Is it appropriate to ask a few questions?

DR. HUDAK: Yeah, I said, Ken, you could sit down while you ask questions while you are asked questions. As opposed to Amy, who we kept up there the whole time.

Pam has gone out. If you need questions on slides, she'll adjust it. So, yeah, it's open for discussion.

Okay. So I have a couple questions. So, clearly, the penultimate slide that shows linear growth of products requiring review has generated this new perspective into review. Clearly needed. I don't think anybody on the Committee can meet six times a year, nor can the FDA probably do six meetings a year on this, but for the products that are awaiting PAC review now, do you have any

estimate of how many of those would be -- come to the PAC under the new review process? That's question number one.

And then question number two would be could you just provide a concrete example on how this would work? Walk through the criteria on your early slides and show us where Precedex, for instance, would fall in terms of it being a reviewed or not reviewed by the PAC?

DR. QUINTO: So in terms of the 44 products based on historical standards, a little bit more than 50 percent of the products would be going onto the web based on my analysis of the data from 2012 to 2015. So approximately 22, or possibly maybe a little bit higher, would go up on the web because those reviews in the current process would qualify for an abbreviated presentation format. So, obviously, the rest would come to the PAC for the -- during the safety meetings.

In essence, really, Precedex, based on the future process, would actually be presented to

the PAC because currently it was presented in a standard presentation format. Therefore, would be brought to the PAC during the safety meetings.

If you would like to superimpose sort of what it would look like, really, the abbreviated presentations to the PAC would no longer be discussed in the PAC safety meetings, and would be put onto the web where all the standard presentations for CDER products would continue to still be presented to the PAC during the safety meetings.

DR. NELSON: And let me just add a little context internally. There's been a lot of effort in trying to use the PAC time efficiently. Part of the reason to institute this process is to start thinking about ways to use the FDA time efficiently.

But we're implementing this under our current sort of workload. So what's not in the presentation is we're going to a system where there'll be meeting every two weeks. Right now it's sort of a boom and bust prior to the PAC

meeting. We're going to go to a standing every-two-week meeting, and these products will be reviewed over the course of the year, and then when they come up for review, they will go to the appropriate PAC meeting, whatever is the next one relative to the work.

We'll be able to look at efficiencies and figure out ways for the use information, epidemiology to further make refinements. But right now, there's not going to be a big change in through put.

Our hope is, if we can find efficiencies, and we have some ideas that are not part of the proposal here, we would have to get the total number of products from 24 a year, meaning two per month, up to 36 per year. We would have to go up by, what's that, 150 percent to even start making a dent in that backlog.

And I will guarantee you right now the epidemiology and use people do not have the staff to be able to do that. And so unless we can find efficiencies -- and this is what I mean by this

continuous quality improvement -- as we implement this, gain experience, reduce the variability, and then begin to look at where our efforts are most appropriately focused, maybe we can make further gains. But as we come up with those ideas, that would then be presented as well so that you have an understanding of what we're doing in the process. But that's the basis idea.

The way it would change what you all do, one final comment, is what I would envision is as we make a decision that this is a low safety risk, meaning it would have -- that that review, same review, gets posted to the web, and then there's an open docket for anyone to comment on that. In the FR notice for the PAC meeting, there would be a list of those that are posted, and anyone could see that.

Whether or not you'd want to know if something goes up, I mean we could even potentially send an email out to PAC members or whatever when something gets posted. But that would allow for the review and comment. That

would save work in our office because we wouldn't have to do any COI. I mean, if someone submitted a comment, we could then evaluate that and then reassess whether or not we should, you know, do something differently relative to what we did, but that's the basic idea.

DR. COPE: Yeah, I just might add to that because you were asking about Precedex, and so, I mean, that would definitely come as a standard because there was a lot of off label use. There were 56 serious adverse events, and a couple deaths. So that would probably come standard.

And what we're doing again, this is our beginning of this. This is the drug products. So typically at each of our PAC meetings, we have about ten drugs products that are coming for their safety reviews, and out of those it varies, like today, for the drugs we just have the two abbreviated talks. It might be as many as four. But it's usually two to four or at the most five, you know, half of those that would have the abbreviated, but the might go up on the web in

this case or whatever.

DR. HUDAK: Okay. We'll take questions. I'll just go sort of around here. Alex Rakowsky.

DR. RAKOWSKY: Alex Rakowsky. Just to follow up on Skip's comments, for the docket, how do you close the loop on the docket? Is there going to be a time frame when the public comments close, and then at what point would you elevate it to a PAC, and what point would you, essentially, close the docket and say we just through this process?

MR. NELSON: Two comments. First of all, I'm not going to comment on when something would and wouldn't be elevated to the PAC because that would depend upon the information that's in whatever was posted to the docket, and I don't really prefer to speculate on what I don't know at this point.

The process would be in my mind since opening and closing dockets is an administrative hassle, my thinking, although we have to have conversations internally, is that there be an open

docket in perpetuity for web posted things, and we would review that docket as part of our normal office processes to see what has been posted so that if something gets posted to a particular product that was listed, then we take that. It would be evaluated by our office, by DPMH. The same people that do the safety reviews would look at that and make a decision as to whether the information presented would merit a change in our approach to that particular product. I mean, that would be the process.

But it would be one docket. Opening and closing dockets for every single product I think would be an administrative nightmare. So one docket for these web-posted safety reviews.

DR. RAKOWSKY: So it would be one docket for all of them. So there'd be a growing list on the docket that would say --

DR. NELSON: Well, for those regulatory junkies, if you've ever gone to a docket, yeah, you can find everything that's been posted in a docket, but I don't expect there'd be a lot in

there because this would be a separate docket from the meeting. There would be a docket, you know, for these web-posted reviews. For every meeting docket, there's an open and closed meeting docket for public comments on what goes to the PAC. Those would be kept separate.

And then we can train you on the docket. I'm thinking a list of training things. One of them would be training on how to use the docket, if you're interested.

DR. HUDAK: Okay. Ms. Celento.

MS. CELENTO: So I have a handful of questions and comments. And Alex, thank you for your question. That was one of my questions.

The first thing I want to say is that the general consuming public has a belief that if something is FDA approved that it is safe. So, you know, I just want to make that comment, and I think everybody here knows that that's what most people think.

We know that most people don't read a package insert, and they just assume that, you

know, maybe the little snippet usually comes on a sticker from the pharmacy will tell them the most important things they need to know to keep their child safe when taking a medication.

The fact that we have this backlog, and I understand how it has come to be, and how it will continue to grow, but that's incredibly disconcerting. When I first started service with the PAC in 2007, I think we were having three to four meetings a year, and we went to two meetings, and I'm not sure if it was a budgetary issue, if it was the fact that as you pointed to, Skip, you might not have enough staff to actually keep up with the workload in terms of, you know, what comes up to go on the list for the year.

So I don't know if you want to comment on that. I can keep going or I can pause.

DR. NELSON: I think the important -- well, let me just say this. Independent of our resources, the appropriate use of resources is a virtue. So I personally think this approach to the extent that it tries to optimize the use of

our time and the PAC time is appropriate.

There was a time we used to do three meetings, but that was a push, and it often meant that we were planning another meeting while another meeting was happening. But that was for a very brief period of time. And as you may recall, we often had time to do four hours on a product. Things have changed.

The issue is not so much our resources. If went to the three meetings, yes, we would need more resources in our office. But what you don't, well, maybe you do see, is that the resources that go behind these reviews are driven as much by the resources in DPMH, resources in the Division of Pharmacoepidemiology, Pharmacovigilence, and resources in use.

To give you an idea, because of the opioid plan, the number of advisory committee meetings that the use staff have to provide data for in the next eight months, 20. All right. So -- and they have no more staff to do that.

So, yeah. Sure, it's a resource issue,

but I would separate that out. If we make appropriate efficiencies, there would be a point if we find efficiencies, and I think they do exist in the system that we've not taken advantage of, and we continue to see it going up, that's the time to then say more resources. But so far we haven't demonstrated that we're totally being efficient in our use of resources now.

MS. CELENTO: Thank you. And I do understand that, and I don't disagree with you in terms of efficiencies. So thank you for addressing sort of the historical picture from my perspective in terms of number of meetings, and number of products.

And to your point, in some of those meetings we looked at fewer products, had longer discussions, and I realize that's really what you're trying to move to in terms of the discussions or the products that are high risk.

I would like to know, and I'm not asking for this data right now, but if you look back over the last two to three years of meetings, and you

apply this new model to the products that were presented either in abbreviated presentations, or full presentations, you know, sort of what the percentage or the products that would have fallen -- that would fall under this new process.

DR. NELSON: Well, Ken presented that data. Basically, it's 50 percent, because we developed --

MS. CELENTO: Okay. So that was retrospective.

DR. NELSON: Well, it was from 2012 to 2015.

MS. CELENTO: Okay.

DR. NELSON: In other words, looking at the data, about 50 percent of the products went through an abbreviated presentation, and the criteria we've developed was not to change those abbreviated presentation criteria. So from that standpoint, the amount of time saved for the Committee here is going -- is not going to be huge, because we're saving a five-minute or a ten-minute presentation.

Instituting this process, we'll be able to see time savings internal to the agency potentially over time. But, yeah, 50 percent of the products would then go to the web without a five minute, one slide, here it is, any questions presentation.

MS. CELENTO: Thank you. And I should be more clear. I would like to see the list of the products which would have been, which would fall under the new process, and it would also be interesting to note when there discussions that actually did take place in the Committee similar to what happened today with Precedex, because that's just my concern --

DR. NELSON: Well, let me just ask -- so the question is if you look at all the past abbreviated presentations, were there any products that weren't abbreviated that, in fact, would have then been taken off that list, and should have gone standard? I mean, that's the kind of question you're asking. I don't know if we have those data.

But, again, if there was information that someone presented that would cause us to rethink that, it would then come back, but the process by which someone would say that would be now through the docket as opposed to saying it at a meeting.

DR. HAUSMAN: Hi. This is Ethan Hausman. I have a clarifying observation. The correct comparator isn't would Precedex have come back. It would be would Skyla have come back.

MS. CELENTO: Okay. So, you know, I've made the comments in terms of what the general public presumes is happening on their behalf at the FDA.

With this new process, and Alex was asking the question, and I understand it's not fully clear, sort of what would the timeline be? Would there be a, you know, a three-months period where the public could comment, public being doctors, parents, patients. How would that be communicated to the public?

And I ask that specifically because, you

know, we have a hard time getting doctors, pharmacists, to understand when a drug shouldn't be prescribed, you know, to a patient in terms of the Sprinkle. You know, we had over 700 prescriptions for children under the age of 1, or 11 months and under that prescription should have never been written, shouldn't have been filled, and, you know, we always struggle with how do people know this? How do doctors know this? How do pharmacists know it? And I'm just concerned sort of to the extent that people don't even understand they can file an adverse event report, you know, the general population.

I'm not sure kind of what the feedback loop is and how consumers get in the game here.

DR. NELSON: So let me give you some thoughts, because we've not drilled down to the point. Clearly, posting a document to the Pediatric Advisory Committee meeting website is not terribly useful because if anyone of you have gone back to try and find documents from previous meetings, you gotta sort of know which meeting

it's at, and that sort of thing.

So what I could imagine is what we currently do on our OPT website is you'll notice links, for example, BPCA and PREA. You know, you'll see all the links to the posting of the medical officer review, the Clin Pharm review. That's all publicly posted.

So I could imagine, although I've not had this conversation with anyone else in my office and so we'll see what happens after the meeting, that we have a section that would be these reports, that it would be very clear that on our website within OPT that you can have access to them, and they would be labeled clearly by product, and not I've got to guess when it got posted type of thing, or go look in the Federal Register, because I agree that would be insane. And it would make sense then to have, as I say, one docket for everything.

And as far as I'm -- if it's an open docket, you could comment on anything at anytime. I mean, if you want to go back and comment on

something, let's say, two years from now that came out a year from now, I mean, you can do that. So there's be no restriction in my mind that, well, gee, that got posted six months ago, and it's now six month later. You can't do that. I mean, it would be one open docket that anyone can go in and say here's the product. Here's my comment about that report that I saw on the website.

So communication I think I agree needs to be clear. And it can't rely on the Federal Register. It can't rely on our advisory committee structure of the website posting. We'd have to come up with something that's more easily navigated by anyone, including people on this Committee and myself because it's very hard to find Advisory Committee material. So that's at least my thoughts.

MS. CELENTO: Okay, thanks, Skip, and Ethan.

DR. HUDAK: Dr. White.

DR. WHITE: I'm going to get myself in trouble. This is Michael White. I stay in

trouble. An open docket for review by the public on scientific reviews seems like at some point is going to overload you with comments that you're not going to be able to keep up with.

It strikes me that would all three -- just as an example. All three of the immunization would fall under this sort of safe and regular review. So the anti-vaccines decide that they're going to inundate you with requests for review because they don't believe vaccines should be given, or somebody has a bad side effect, not necessarily one that would be viewed by the Committee as something that requires a lot of review, but still would fall under this general thought process that this is a safe drug. But they don't believe that, and they get some members of their church or whatever, and this gets propagated throughout the community.

I think your efforts at abbreviating the process are excellent. I'm not sure that an open documents for public review and comment to spur the process forward is the best choice. Maybe I'm

wrong. But I think a process whereby the members of the Committee could go in and review, and if they requested, then bring it to Committee might be a little bit easier for you to deal with going forward in the future.

DR. NELSON: Couple comments.

DR. WHITE: Okay.

DR. NELSON: First of all, given the number of public comments we get are at Advisory Committee meetings, I would look forward to the possibility that there would be greater public interest in the work that goes on here. So we don't get a lot of comments.

So second of all, these need to be publicly posted. To not post them publicly, and to provide a private docket for committee members would actually be a violation of the Federal Advisory Committee Act because we would not be screening for conflict of interest.

So we could not present it to you and not have the public comment.

DR. WHITE: Okay.

DR. NELSON: It needs to that. I've got a few other comments. Let me finish, Michael.

DR. WHITE: Sure.

DR. NELSON: Vaccines, the FDA is on record to say we don't think vaccines ought to be part of this process, and we've asked for --

DR. WHITE: Okay.

DR. NELSON: -- there to be legislative fixes to that.

DR. WHITE: Okay.

DR. NELSON: And this is not being applied to vaccines right now anyway. This is a CDER proposal.

DR. WHITE: Okay.

DR. NELSON: CBER as looked at it. We've not had conversations. This does not apply to vaccines.

DR. WHITE: Okay.

DR. NELSON: And so we're not opening that door, basically, and the -- so from that standpoint, this is purely a CDER process. We would have the conversation CBER. FDA is on

record as saying the vaccines ought not be part of this process because they are part of multiple other processes that review safety in much more detail.

DR. WHITE: Okay.

DR. NELSON: So those are the thoughts.

DR. WHITE: I understand the concern -- help me, because maybe I don't understand. The way we currently do this, the data is always available for review. If any of the members have questions they can call for it to be presented at a meeting where everyone has been cleared. So --

DR. NELSON: We're not changing that.

DR. WHITE: Okay. I don't think it needs to be hidden from public by any means. That's not what I'm proposing. I'm just looking for a mechanism that allows the members of the Committee to go through it and call for it to be brought for a full review if there's a question.

DR. NELSON: You would have -- you would have the right to do that. If you look at the designated abbreviated review, I mean, that's --

DR. WHITE: Right.

DR. NELSON: You would have the right to publicly comment on the docket to say, you know, I think this ought to be X, Y, and Z. I will say the only times that a designated abbreviated review have been vetoed, have been issues that are unrelated to drug safety.

DR. WHITE: Uh-huh.

DR. NELSON: It's been because there's some other issue. And so we would look at that and say, well, is this really a drug safety issue. I mean, it could be some other broader issue that ought to then be examined in some other venue, or in some other mechanism than just bringing that drug back.

So I don't want to speculate about (a) products, (b) what kind of comments may or may not result in that, but it would be evaluated. I mean, the Skyla example, I think that's very interesting, but the answer there is not adverse events on Skyla. The answer there is a clinical trial that looks at bone mineral density for

progesterone products, and can you figure out a way to do that separate from an adverse event report for Skyla. I mean, that's what I heard there, and that's what I think we need to think about.

So -- but that kind of comment, I would hope that the members of the Committee would look at these reports and provide that sort of advice, but rather than taking up time at a meeting, it would be through that process.

DR. WHITE: I'm all in favor of doing that. I'm just trying to get a better idea of my function.

DR. NELSON: And we would train you on -- I mean, submitting to the docket is not that hard.

DR. WHITE: Yeah. Okay. The other -- in the interest of trying to save some of your time, is there anyway we cannot have to do all these annual reviews of HUDs for the annual distribution number?

DR. NELSON: I'm glad you asked that

question, because similar to the vaccines, if you look at the device legislation, it has the word, "annual," in it. So we haven't -- I mean, we've had discussions about whether that's useful or not. I think there's one product on today's agenda that has no pediatric data. There's another product scheduled for September. There's no pediatric data. But we have to sort of bring that because of that word, "annual."

We've not talked to our attorneys yet to see if there's some way we can twist ourselves around that word, as opposed to a legislative change that might, for example, take the word, "annual," out and make it periodic or something. I mean, people think it needs to be reviewed, but does it have to be annual?

So the FDA is in favor of that as well. We don't have as much flexibility on the devices because of the presence of that word.

DR. WHITE: Thank you.

DR. NELSON: But I would love it to be changed.

DR. HUDAK: Dr. Turer.

DR. TURER: So I wonder about the process of FAERS, and whether there could be efficiency in at least thinking about how to wisely incorporate electronic medical record imported data so that you had better quality data regarding when drugs were started, when they were stopped. Also, it seemed that the databases we're pulling from are not pulling children's hospitals. So some of these procedures and some of these devices they're in use. The children may not be in clinical trials, but there's data there.

So some of the efficiency I wonder could be in changing a system thing that may be introducing efficiencies, inefficiencies. It wouldn't get at problems beyond the U.S. because I don't know how we could do this necessarily with Europe, but, certainly, I think we could do it with EMRs.

DR. NELSON: No, absolutely. I mean the FDA Sentinel system is an attempt to harness those, and the extent to which that can be

developed to where it can come in. I mean, it's -- you know, once we put in a process -- I mean, part of this is putting in a process by which we can then say, well, are there better ways of doing this.

But those are very broad issues that extend beyond pediatrics in terms of the development of electronic health records and feeding into adverse event systems. Even in some electronic health records, adverse events are not captured very well, because it's designed for billing. And unless that adverse event results in the physician being able to charge more money to do something at a hospital, it's not going to be captured. So big issue. FDA wants to work on that broadly. The Sentinel system is designed to do that. We have conversations about how pediatrics can be at least on that train, but that's probably a, I mean, that's an aspirational goal. Absolutely, it would be great.

DR. HUDAK: Dr. Cunningham.

DR. CUNNINGHAM: I just had a specific

-- I'd like to go back and look at Slide 15. I'm afraid I might have misread it. But if not, I want to talk about it.

(Pause)

DR. NELSON: That's what you're currently doing. But if you go to 14, 15 is simply an easier way to read what's on Slide 14.

DR. CUNNINGHAM: Sure. And it may be, it may just be semantics, but if we look at number six on the next slide -- I'm sorry. 15. So it says no or few pediatric drug related deaths or SAEs. So are we really saying even if there are a few pediatric drug-related deaths that that can remain in the category of abbreviated presentation? I think it may just be semantic, because I don't think that what we're wanting to say.

DR. NELSON: No pediatric drug-related deaths or few SAEs. I mean, it's meant to capture what's on the prior slide.

DR. CUNNINGHAM: I mean, part of -- I mean, I hear your comment. Part of the challenge

here, and this is also what we would put in the review, is why did FDA decide this could be posted and not presented.

DR. NELSON: So there would be that clear description of that. And the reason we call it current factors is it wasn't clear to be that it could be reduced to an algorithm. But, clearly, in the report, there would be a clear statement about why we believed using these criteria that it could be web posted so it would be transparent. And if someone disagreed with that, they could disagree.

Ken, do you have anything else to say on that one criteria?

DR. QUINTO: No. Literally, it's from one of the boxes in the diagram that's very difficult to read in the previous slide, Slide 14. It's the second row. Second one from the -- not the far right one, but the one closer to the center from the right.

DR. MURPHY: Dianne Murphy, and I just want to -- you know, I think what you're seeing

there, we tried to reduce that, and if you go back to our really initial data, it says no deaths or few SAEs.

DR. CUNNINGHAM: Now when I read the fine print, that makes sense.

DR. HOEHN: Can I ask a follow-up clarifying question? So look at that for number seven, you would require all of the above, not just one?

DR. NELSON: To look at which?

DR. HOEHN: For criteria factors for abbreviated presentations, you'd want all of them to be true that death was attributable to an underlying disease? You wouldn't just pick one of them. You'd want all seven present, correct?

DR. QUINTO: Actually --

DR. NELSON: And it wouldn't necessarily be all seven. But, I mean, obviously, it probably wouldn't be just one. I mean, again, I didn't want to -- I mean, to sit down and create a algorithm out of this, I tried to do that once for our office, and everybody rejected it because they

just didn't think the way I did, I guess.

But it's not going to be just one. It would have to be a combination of those. But that would be clearly presented. I mean, there are situations where HIV would be an example where on one you may have -- and there's other examples where there could be clearly disease related deaths, and that would be clearly -- again, the reviews are going to be posted. It's not as if these are no longer going to be reviewed. So from the Committee perspective, it's just going to be the added, call it inconvenience, of just, you know, needing to go to a link to look at the review, and then provide a comment.

Now, you can even comment to us by email, but then we would put it in the docket. I mean, we get -- Marieann gets comments by email she has to put in the docket, so it's not as if there won't be mechanisms by which you can express concerns about the reviews.

DR. QUINTO: And this is Ken Quinto. Just for clarification, there are currently three

abbreviated presentation formats. The first two need to be met in order to have a justified abbreviated presentation. Three through seven -- actually, three through five is for an abbreviated presentation, and three through seven is for a designated abbreviated presentation format. I just tried to get it all on one slide for ease of reading. But thank you.

DR. HOEHN: But if a Committee member reviewed it online, could they request that it go to full Committee?

DR. NELSON: A Committee member could make any comments they want, and we would evaluate whether taking it to full Committee was appropriate based on the information provided. So, I mean, it -- but I wouldn't want to say that it would always go to full Committee simply because a Committee member said that.

DR. HUDAK: Dr. Kaskel.

DR. KASKEL: Rick Kaskel. So what one of the things I've noticed lately is with the internet assisted reviews that we're asked to

participate in where we're given a number of grants and guidelines how to review online with a timeline to make the comments, open discussion, respond, and the close discussion, and a summary.

Seems to work. Seems to help out. Is this another way of looking at some of this process where we would have a timeline to review specific applications, and comment, and have a back and forth, and then summarize?

DR. NELSON: I mean, we've had internal discussions about whether or not you all might appreciate, so let's imagine if half -- if we're reviewing 24 a year, and, roughly 12 per year would go through this process based on past statistic, statistically that would mean you'd get an email once a month saying report on Drug X has been posted to the web. Here's the link.

I would imagine putting into that how you could provide comment on that which would -- you know, the FDA doesn't have a process which you can do that other than through a docket so that the comment -- and basically, that's the way you

would provide that is through the docket.

Now, everybody can see that. That's publically accessible. So, you know, I could see doing that so that it would be easy. It could be the link to the docket so that you just click, and you click on it, read it, click on the link, and then if you have something to say, you say it. And then, you know, that would be the process.

DR. KASKEL: But in that process, would there be room then for back and forth, an open dialogue?

DR. NELSON: No. If there was, if it was warranted I don't see why not. But the challenge is having that -- I mean, I'd have to check with people to the extent to which that should need to be publicly accessible, and the extent to which we then respond to a docket comment. I mean, there's some legal issues that I would have to check into about how we structure that process so that it's aboveboard.

DR. KASKEL: I mean, in the NIH internet assisted review only people commenting are the

reviewers.

DR. NELSON: I know, but they don't -- that's not a Federal Advisory Committee Act function. So that -- I mean, I need to think through and make sure that we're doing it in a way that's appropriate in the context of the Federal Advisory Committee Act.

DR. HUDAK: Dr. White, one last comment.

DR. WHITE: It seems to me that one and three could just be eliminated, and just say drugs that are used to treat childhood diseases for children under such. Are you going to bring back a refined version of this to us?

DR. NELSON: No.

DR. WHITE: Or is the plan just to proceed if we agree? If we agree to it, we're going to go with what the proposal is?

DR. NELSON: We're proceeding with this.

DR. WHITE: Okay.

DR. NELSON: And, you know, I mean, this again, we haven't developed a list for this group. I mean, this was simply taken under some

redundancy. And, again, this is not an algorithm, but, you know, the intent is to start implementing this -- you know, the September meeting is sort of a hybrid, but let me -- you know, one of the reasons why you haven't seen as many abbreviated reviews on today's agenda is because we did a little bit of moving around by taking products we thought would go abbreviated and delaying them in anticipation of instituting this, and there's other efficiencies we can find, for example, things that have gone abbreviated in the past if there's no new SAEs, could probably then go through this process.

DR. WHITE: Now the process is that this will be put on a docket and stay there in perpetuity. How often will these drugs be reviewed again? They're just going to follow the standard --

DR. NELSON: We're not changing -- I mean, we can't change the regulatory requirement that review this at least 18 months after --

DR. WHITE: So how do you foresee a drug

being reviewed a second time and leaving the first docket open?

DR. NELSON: Well, it depends. I mean, if a drug comes through standard review at this meeting, it's not part of that continuously open docket. It's at the meeting. There's a docket for the meeting.

DR. WHITE: Right.

DR. NELSON: It comes a second time, then the question would be does it meet or doesn't it meet. So there are products that have gone for abbreviated reviews in the past. I think there's a handful. I don't know. Maybe up to 10.

DR. QUINTO: A couple from my research so far.

DR. NELSON: Yeah. So that where it was abbreviated before, and so one question is if we do -- if we look at the SAEs and we don't see any, presumably it would meet this again.

DR. WHITE: Okay. You just post a second -- a second docket, or add it to the -- I guess that's detail --

DR. NELSON: Separate the docket. The docket is just a mechanism by which you provide comment.

DR. WHITE: Okay.

DR. NELSON: Right? There would be a second review. We would not be changing the review requirement. So if it came a second time, it would get a full review just like we do normally. The PPIs, I'm sure, will be back. I suspect they'll come back standard given all of the issues that PPIs -- a whole second review. None of that's changing.

DR. WHITE: I know. But with this particular process, you're just add it at the bottom of the list and send us an email for the next time it's reviewed under this process?

DR. NELSON: What I would imagine is we'll have a web page with these reviews, and we haven't talked about how to structure it. I could see a product, and then review one review, to reviews, three reviews, multiple.

DR. WHITE: Okay.

DR. NELSON: The email that you would get if you -- I mean, I'd like a sense of the Committee if you'd like an email, if something gets posted it would simply link the review that's current, and then you'd go in and you could look at and then could comment.

So, I mean, if -- I personally would prefer that as opposed to an FR notice that lists half a dozen products that have been posted in the last months. And in talking with our staff, they think that would be easily doable.

DR. WHITE: Okay.

DR. NELSON: You know, that's the idea. We're not changing the review and the documents. I mean, there's not a change in what we actually produce at this point, although with efficiencies, I'd like to see us -- we might make changes as we develop that, but that would be -- we'd come back to you if we saw efficiencies to get feedback on that.

Does that make sense? I mean --

DR. WHITE: Yeah, I think so. The

process you're seeking seems to be a good one. I agree with what you're trying to implement. Just the details are not quite clear in my head. But it looks like it's a process in evolution so the details are not there yet.

DR. NELSON: Yeah. I mean, there's a transition, and in September we can see, we can talk about it more. I mean, we're implementing at least the every-two-week meetings starting I think in June, July? June? Somewhere around there, and we'll see how that goes. So the September meeting is not going to be sort out by this process. Whether anything pops up that we would do this, you know, that'll start evolving. As I said CQI, I mean that, you know, continuous quality improvement. That means it's not fully worked out at the start. We're putting a process in place that reduces variability, establish some consistency, and then we can make modifications that make sense as we go along. So that's the idea.

DR. HUDAK: So thank you, Dr. Nelson.

DR. NELSON: And let me just say Ken has put an enormous amount of work into this, and so all that has been data driven, as you can see, and I want to just publicly thank him for work that he's put in to putting this proposal together.

DR. HUDAK: So we do not have a motion on this, but I think for the record, we can record the sense of the Committee as being supportive of this effort to try to be more efficient in these reviews, and to really concern the Committee with those reviews that are more important in a more timely way, and we accept that in this CQI motion going forward that there will be opportunity to modify as needed any of these processes.

So I would think that by the meeting next April we might be able to have an opportunity to assess where we are with this process.

DR. NELSON: No, I think so. So the process instead of scheduling a lot of meetings on products four months before a PAC meeting in six months, I mean, we'll be sliding products in every two weeks, and so I'm presuming that by the

meeting in the spring of 2017, that we'll begin to, you know, that we will have begun to see the impact of this process. But whether it'll be fully transitioned I think we'll just have to see how that works out. But, yeah.

DR. HUDAK: Okay. Very good. So just another little aura of housekeeping here, we have the necessity to take a small break at around 4:30 before the CDRH presentations. Let's move on to sort of see how many of these next presentations we can get through. If we have a need to do a biological break before the CDRH --

MS. WEINEL: I'm sorry. 3:30.

DR. HUDAK: 3:30. Before -- I'm sorry. 3:30. Right. Before our schedule. So we have Dr. Khurana here? Excellent. So you are here from the Division of Pediatric Maternal Health, Office of New Drugs, and CDER. And we have two presentations we'll hear. One is on Vyvanse, and then we'll move to Symbyax.

DR. KHURANA: Do my colleagues want to come to the table?

DR. HUDAK: Yes. We have the ever train of new colleagues coming to the table, so we have four new people. Would you introduce yourself to the group?

DR. CHENG: My name is Carmen Cheng. I'm a safety evaluator from DPV.

DR. DIAK: Ida-Lina Diak, team leader, division of pharmacovigilance.

DR. FARCHIONE: Tiffany Farchione, deputy director division of psychiatry products.

DR. WONG: Jennie Wong, drug use analysts.

DR. KHURANA: Thank you. Good afternoon. I'll be presenting the pediatric focused safety review for Vyvanse. I'll be following the same general outline as the other presenters and we'll start with background information on this drug.

Vyvanse is a CNS stimulant drug product containing lisdexamfetamine and is indicated for the treatment of ADHD in both adults and pediatric patients down to 6 years of age, and for treatment

of moderate severe binge eating disorder only in adults. The recommended starting dose for treatment of ADHD in patients 6 years and older is 30 milligrams once daily in the morning.

Vyvanse's April 2013 approval for maintenance treatment of ADHD in pediatric patients prompted this safety review. Following initial U.S. approval in 2007 for ADHD treatment in pediatric patients 6 to 12 years of age and adult approval for the same indication in 2008. Pediatric use was expanded in 2010 to include adolescents 13 to 17 years of age. The adolescent approval prompted a pre-mandated safety review of lisdexamfetamine that was presented to the PAC in September 2012. With the April 2013 approval for maintenance treatment of ADHD in pediatric patients 6 to 17 years of age the sponsor fulfilled their pediatric study requirements for all relevant pediatric age groups.

I'm going to spend the next few slides highlighting relevant safety information currently included in Vyvanse labeling. The box warning is

identical to those for other drugs in the CNS stimulant class and warns against the potential for abuse and dependence. Vyvanse is contraindicated in those with known hypersensitivity to amphetamines or to other product components. The concurrent use of monoamine oxidase inhibitors is also contraindicated.

Vyvanse labeling contains the same class warnings and precautions as that for other CNS stimulants. This warnings, again, highlights the potential for abuse and dependence, and also include language strengthened based, in part, on previous PAC recommendations to address safety concerns about cardiovascular, psychiatric, and endocrine adverse events.

Data from two pediatric studies were included in the efficacy supplement which was approved in 2013. One study offered additional support for the efficacy of Vyvanse in the short term treatment of ADHD in pediatric patients. This was a randomized, double blind, placebo and

active control study, and 336 patients, 6 to 17 years of age with ADHD. The safety profile of Vyvanse in this study was similar to the overall safety profile described in current product labeling. Data from this study were included in the clinical studies section of product labeling.

The other study was used as the basis to approve Vyvanse for maintenance treatment of ADHD in patients 6 to 12 years of age. This was a 26 week study and 276 patients with ADHD. Patients who had been stabilized on 30 to 70 milligrams of Vyvanse during a 26 week open label phase were then randomized in a double blind manner to continue their stable dose or receive placebo. Results showed a significantly lower proportion of treatment failures in Vyvanse treated patients compared to placebo at the end of the six week randomized withdrawal period.

Although the study was designed such that only patients who tolerated the drug in the open label phase were randomized into the withdraw phase. The adverse events reported during the

study were consistent with the known safety profile of lisdexamfetamine. Following Vyvanse's pediatric approval for maintenance therapy of ADHD, the pediatric use subsection of Vyvanse labeling was updated to cross reference to the relevant sections and product labeling where information from both pediatrics studies was added.

Now let's look at the use of Vyvanse. This graph provides the number of pediatric patients who received a dispensed prescription for lisdexamfetamine from U.S. Outpatient retail pharmacies from July 2012 through June 2015. As you can see, approximately 1.1 million pediatric patients received a dispensed prescription in each 12 month period which was examined. The vast majority of pediatric use during the entire time period was in the approved school age population of 6 to 16 years. Use in the unapproved pediatric population less than 6 years of age remained low and stable.

During the same time period,

approximately 29.2 million lisdexamfetamine prescriptions were dispenses from U.S. outpatient retail pharmacies. Psychiatry was the top prescribing specialty at 31 percent, followed by pediatricians at 26 percent, and family practice specialties at 22 percent. According to an Office Space Physician Survey database, the most common reason for use in all the pediatric age groups, even in those less than 6 years of age, was attention deficit disorder.

Now we'll look at the pediatric focused adverse events for Vyvanse since the last review. For the purpose of this review, we focused on reports describing all adverse events with any outcome in patients less than 6 years of age since Vyvanse is not approved for use in this pediatric population. We chose this strategy based on discussions at the 2012 PAC meeting where some committee members recommended including patients less than 6 years of age in routine adverse event monitoring due to the increased off label use of Vyvanse that was noted in this population at that

time. We also focused on reports of serious unlabeled events in patients 6 to 17 years of age for whom the product is approved.

We identified 40 reports in patients less than 6 years of age, including one fatal report. We identified 389 reports of serious unlabeled events in patients 6 to less than 17 years of age, including 24 fatal reports. Two hundred and fourteen reports were reviewed and excluded. The chief reasons for exclusion were duplicate reports and reporting of labeled adverse events. There were a number of other reasons for exclusion which are listed on the left side of this slide. This resulted in the selection of 215 cases which were the basis for this pediatric focused safety review.

Thirty cases, including one death, occurred in patients less than 6 years of age. The remaining 185 cases described serious, unlabeled events including seven deaths in patients 6 to less than 17 years of age. Eight patients died. For two patients the reported

cause of death was unknown, and for one patient an alternative etiology was reported as the likely cause. We could not assess causality in the other five patients for whom suicide or homicide was reported because the case narratives either contained too little clinical information or described the presence of other factors which may have confounded the assessment such as a psychiatric history, non-compliance with a prescribed antidepressant, or a psychological stressor.

Reports of suicidal ideation and behavior associated with Vyvanse use have been discussed at previous PAC meetings where FDA has shared epidemiological and controlled clinical trial data that have not suggested increased rates compared to the general population or in patients taking stimulants compared to placebo. Some of you may be familiar with this slide which was presented at the September 2012 PAC meeting that shows results from an adjudicated analysis in which we found no increase suicide related events

with Vyvanse use. At a 2006 PAC meeting we had presented results from a meta-analysis of clinical trials for ADHD stimulants conducted by FDA that did not identify a signal for increased suicidal ideation and behavior with Vyvanse use.

We identified a total of 29 non-fatal adverse events in patients less than 6 years of age. Seventeen were labeled events, listed on the left side of this slide, and seven were unlabeled events which are underlined and listed on the right side of this slide. In addition, four cases of accidental exposure were identified. Two of these cases reported labeled events while the other two cases did not report an adverse event. There was also one case of overdose in which the affected patient developed both labeled and unlabeled events.

We identified 178 non-fatal cases describing serious unlabeled events in pediatric patients 6 to less than 17 years of age. The most commonly implicated system organ classes are listed on this slide, and I'll describe the most

commonly reported preferred terms within each of these system organ classes over the next few slides. We did note that there were cases describing isolated preferred terms belonging to 14 other system organ classes, but these cases did not provide enough information for us to determine if potential safety signals existed.

The highest proportion of cases involving psychiatric disorders reported suicidal or self-injurious thoughts or behaviors. The majority of this cases involve concomitant psychotropic drug use or underlying psychiatric histories or did not contain enough information for assessment. Nearly half of cases involving nervous system disorders reported loss of consciousness or syncope, both of which are not labeled events. Half of these case reported that the patient underwent a cardiac evaluation which was normal. Further evaluation is recommended in product labeling for patients who develop unexplained syncope during Vyvanse treatment.

Four cases reported the preferred terms

of incoherent speech disorder or unresponsive to stimuli in patients ranging from 6 years to 13 years of age. But these cases showed no consistent pattern on clinical review. Isolated cases for other preferred terms are listed on this slide. More than half of cases involving cardiac disorder reported chest discomfort of chest pain. Nearly half of these patients received further evaluation as recommended in product labeling. Among the patients who received further evaluation, one patient was noted to have a heart murmur while the remaining patients had a negative cardiac evaluation. Less commonly reported preferred terms from the cardiac disorders system organ class are listed on this slide. Adequate assessment, in many of these cases, was complicated by the patient's medical history of concomitant drug use.

We identified a possible signal for alopecia associated with lisdexamfetamine. Three cases reported significant hair loss. Two of the three cases reported hair growth following the

discontinuation of lisdexamfetamine. Although this is a small number of cases we noted them because other ADHD drugs are labeled with this adverse event. Alopecia is not currently a labeled event for Vyvanse.

This concludes the pediatric focus safety review for Vyvanse. We identified a possible signal for alopecia that will undergo further FDA review with results to be presented at a future PAC meeting. We recommend continuing ongoing surveillance. Does the committee concur? I would just like to thank everyone on this slide for their help with this presentation.

DR. HUDAK: Thank you. We'll open up for discussion. Dr. Mink?

DR. MINK: Do you have any information about whether the alopecia represents true alopecia or whether it could represent trichotillomania?

DR. KHURANA: Do my OSE colleagues want to comment?

DR. MINK: So hair falling out versus

hair being pulled out?

DR. CHENG: The cases did not specify specifically the patient was pulling the hair out. The cases mentioned no other changes in shampoo or anything else, so I would suspect if there was this behavior noted it would have been reported, but in the three reports that was not noted.

DR. HUDAK: Dr. Towbin?

DR. TOWBIN: I was just wondering, and this might be a time to summarize this long email that came last night just so that people know what was there, so if you don't mind I'll just try to offer you a brief summary. It is a seven page single spaced email, so there's a great deal there. It comes from Andrew Thibault who is part of the Parent's Against Pharmaceutical Abuse.

It opens with a series of concerns that lists actions by the FDA against manufacturers of stimulant drugs related to some of their marketing materials that they believe overstated the long term benefits of these agents. He then goes on to talk about his concerns about these agents,

particularly this one, creating suicidal ideation, violence, and he states his concerns about the committee being given misleading information.

There's a discussion about his views, in very strong terms, that these are drugs that cause these kinds of problems. Then he asks that, based on the available evidence, that the PAC recommend to the FDA that it maintain the label advisory that Vyvanse safety and efficacy in pediatric patients below the age of 6 have not been established. So that's the summary here.

I'm happy to offer my own personal comments about this. Speaking now, just for myself and certainly not for the PAC or for the National Institute of Mental Health. I think that the concerns that he raises are legitimate concerns. That is in prescribing these agents to patients. Patients need to be monitored closely. These are not agents that should be given in a cavalier way. I think for a while we've been talking together about reconciling the product labeling of newer agents with some of the older

agents because, of course, things like Dexedrine, dexamfetamine, or methylphenidate, Ritalin came on at a very different time, and so the labels do actually still show some differences but no large ones.

The best example is that the label for Adderall includes aggression as one of the psychiatric risks effects where that does not appear in the label that we were supplied with lisdexamfetamine. But I think the bottom line here is that the concerns about agitation, suicidal ideation, psychosis, increased irritability, aggression. These are side effects that are well-known to people, at least in child and adolescent psychiatry and neurology who prescribe these agents. I don't think that Mr. Thibault's comments would raise any additional or new concerns beyond what's already in the label.

I think it is clear that the use of these agents in use of children under 6 is much more controversial than in the populations that have been studies thoroughly in placebo controlled

trials. So that's a kind of summary of my comments and reflecting on what he said.

DR. HUDAK: Dr. Dracker?

DR. DRACKER: Bob Dracker. I think any discussion that involves the use of stimulants for children with ADHD has to be put in context of comorbid conditions. They're very prevalent in this population as well. I mean, upwards of 50 percent have comorbid conditions that cause a lot of the other events. Whether it's suicide, homicide or other behaviors. There's a clear cut different in dexamfetamine use and its effects on children, especially adolescents versus children, with regards to aggression. I'm very hesitant about using it.

The other thing that I think most physicians, at least pediatricians, prescribe to is the concept of minimal effective dosing. We use the least amount necessary for the effect seen. I think, in general, physicians, again, pediatricians who have been asked to do much more of this pharmacotherapy than we've ever done

before, have been very careful about how we use these medications. I think we do so fairly responsibly for the most part. Thank you.

DR. HUDAK: Yes.

DR. RAKOWSKY: Alex Rakowsky.

DR. HUDAK: Dr. Havens first.

DR. RAKOWSKY: I didn't hear. Sorry.

DR. HAVENS: Slide 18 please. So suicidality is not in the label currently. Did I read that wrong or?

DR KHURANA: No, it's not in the label.

DR. NELSON: That's correct. It's not.

DR. HAVENS: So how many times does suicide need to show up in these post-marketing reports before it makes it into the label in a phrase other than find out if there's a family history? As I did a find on the label that was supplied to us in the document, the only place that suicide shows up is to ask if there's a family history of suicide. I'm impressed at the number of times suicide or aggressive behavior shows up in the reports. The statements that

we've heard here that focus on the fact that these people who know a lot about this drug would be careful about that perspective, and then the mismatch with what's in the label. So then the question I would ask of the FDA is what level of evidence is required to get something into the black box about something that seems to be the most prevalent finding in these reports?

If we're not going to act on them with this level of support what would act on? It's Peter Havens, but I think you know that.

DR. KHURANA: Does the division want to respond?

DR. CHENG: Even though there were 52 reports reporting suicide or behavior or ideation when I evaluated each of the cases there were cases that reported medication was discontinued. There was a negative de-challenge. So when the medication was discontinued event did not improve or cases where there was preexisting history of depression of psychiatric behaviors or the social factor. So even though there were 52 cases when I

evaluated the cases the final number were not that high. As far as the threshold I would defer that question.

DR. FARCHIONE: So when you looked at the number of cases and you got down to the end and looked at the number that you thought may possibly be related how many did you end up with?

DR. CHENG: I had 12 cases possible, but even those they were missing past medical history, concomitant medications, and then another six cases with possible time factor event happen after the medication. But still, within those, they were also missing information. So less than half of the cases where it was even possible, but --

DR. FARCHIONE: So basically a total of 12 cases where you couldn't rule out a rule for Vyvanse, but at the same time because you didn't have enough information related to past medical history, whether these kids had an underlying major depressive order or something else like that. Again, you know, you mentioned comorbidity earlier, it's very difficult when we're dealing

with post-marketing reports to try to come up -- you know, we have to deal with what we're given, and we don't always have enough information to make an adequate assessment.

When we go through and look at it like we did with -- you know, there's the slide where we looked at all of the different drugs over time and everything, doesn't look like there's an association. This is a really big deal if we put it into the label and we want to make sure that it's real before we scare everyone away from using something that is so effective to treat the condition for which it's indicated.

DR. HAVENS: Oh no. I'm very supportive of that. I'm just asking how do we quantify -- how do you know when you've reached a number of cases that reaches this level or what are the other data that we on the committee should be asking for in response to this potential for a signal that's not adequate to change the label? But hearing from professionals on the committee who say well, duh, I always ask about that. What

are the other data points or how do we help with that?

DR. FARCHIONE: I mean, I think that, as with anything, when we're looking at the post-marketing reports the more detail we can get in those reports the better. If people would submit those reports and say, you know, that this patient was perfectly fine, just ADHD, no other past psychiatric history. They started taking this medication and five days later became despondent and started having suicidal ideation. We stopped the medication and he got better. That's pretty compelling. We don't have anything that looks like that.

Obviously, you know, that would be, depending on your perspective, best case or worst case scenario. But, you know, best case for the data. The chances we're going to get those cases, even if those cases exist is pretty slim given the frequency with which people actually report these things. So, you know, the most that we can do is just encourage people when they do submit these

adverse event reports to give us as much detail as possible and actually fill in all of the fields that are available.

DR. HUDAK: So Dr. Cnaan. Then Dr. Hoehn and then Dr. Towbin.

DR. CNAAN: Avital Cnaan. So one of the things that concerns me is that we've all said repeatedly with regard to just about any drug that appeared here is that these databases under report. That it's a voluntary report that more often than not we don't get it or we get it with too few details, etcetera. So I'm looking at these numbers and I'm asking myself the question how many more are there? Then I look at the label and I don't know what the answer is. I'm sort of posing the question.

I don't know what the answer is, but right now in the label it only appears in abuse and dependence. It doesn't appear as a potential side effect, not anything else. And in it appearing there it's almost stigmatized so that it might cause even more underreporting because if it

happened it must have been abuse. So I don't know that. It's a conjecture. I'm not saying that I have the facts or the data. But I'm saying that we have here maybe a little bit more of an issue than we have. I think needs to be discussed and considered what to do about it.

DR. HOEHN: My question was about what we have in terms of population data. Because I don't know if there's rates of suicide among kids with ADHD that are on meds versus not on meds. Because it seems like you could take a random sampling of kids with ADHD, not on meds, and you might find similar numbers. So I just didn't know if there was anything in terms of a suicidality rate for ADHD kids, sort of on meds, off meds? If there was anything that says, hey, this is what goes along with having ADHD? I don't know if anyone has that data? I don't know if that question made sense. It made sense to you.

DR. TOWBIN: So, Dr. Mink, do you want to say something about this before I reply? Because, of course, you and I share an interest in

the same organ.

DR. MINK: Just to make two comments. One, again, the shortcomings of a voluntary reporting system. I might argue that suicide might be reported to a greater degree than things like "Loga Ria" because it is so dramatic, and so there may be, actually, compared to other things a higher likelihood of having suicidality being reported than, say, an ingrown toenail just because of that.

I think a big factor that is important in considering all this data is the rate of misdiagnosis, and that as has already been alluded to, individuals who have underlying mood disorders may respond in a very different way. In the clinical trials that were done there were very clear strict enrollment criteria, and I think we have very good data from those and from other population studies. Whereas now, in the post-marketing surveillance we don't really know how many of those individuals, those when that data are available I know you consider them.

But I think, again, if it's a question of what's the safety of the medication in labeled use as opposed to what's the safety of the medication in appropriate use versus safety of the medicine in situations where we don't really know. I think those are different questions.

DR. TOWBIN: So if I may, just a few comments on both of those. Dr. Mink is his usual wise and eloquent self. I think there are several issues that I might point out here. So one is the best evidence for this would come from clinical trial data where we have similar populations that are randomly assigned to either one drug or another in an active model or to a placebo. The problem about most clinical trials is they exclude people with suicidal ideation or a strong history of suicidal ideation, so that's not a very good reflection of what may be going on in the community, in the wide community. And so many of us would be concerned about the kind of monitoring that one would do with a patient who had a history of suicidal ideation when starting a drug like

this.

The second thing to say is that the population of children who have ADHD, as Dr. Dracker pointed out, is a very muddy one with a lot of comorbidity, anxiety, depression, developmental disorders. All get brought under this umbrella. And, indeed, those populations may respond differently to these drugs than individuals who would have, so called, garden variety ADHD without comorbidity. The rates of irritability and the suicidality that may follow in the context of irritability is very high if you just look at children with attention deficit hyperactivity disorder. Irritability is probably a comorbid feature in 30 percent to 35 percent of those individuals. Those are the same, I think, subgroup that may surface with suicidal ideation.

What was pointed out in the FDA response we just heard where something that's very clean that has no prior history and then has the experience of only suicidal ideation soon after starting a drug at a reasonable dose, and then

ends with de-challenge that would be stronger evidence. These are mostly associations and dissociation and causation are not the same thing, as we all know so well.

So my view about this is, of course, I'm deeply concerned about suicidal ideation in this population. One follows patients who are starting these medications closely and carefully. I think there's a risk of people being cavalier about these agents and that's a problem. But I think that as long as one recognizes that these are serious and important interventions, and recognizes the comorbidity I actually think that the labeling itself, which cannot really govern practice, would not increase the seriousness with which people would regard this. I actually don't see through a label change that you could get people to be more careful about this.

DR. HUDAK: Okay. I had saw Dr. Havens first.

DR. HAVENS: Well, I think the discussion that you've just had gets to a crucial

question that we might ask about post-marketing surveillance and its use and what we're supposed to do with it. Given that in a randomized trial that a large proportion of the population who might have had prior depression or suicidal ideation would be excluded, and then the produce is labeled as such.

Once it moves into general use where it might be used for people who have those preexisting conditions then is this kind of system useful in allowing us to strengthen our statements in the label or is there another place where you see it appropriate to strengthen the statement that it should -- I hear the professionals in the room saying, I wouldn't use it if you were depressed or had suicide. You would be very careful about it. You would maybe meet with somebody much more frequently after you started it. There would be special -- and none of that pertains in the label. What is the best mechanism to get that into general public view?

DR. HUDAK: I would go to Dr. Dracker

and I'll go around the circle.

DR. DRACKER: Interesting, it looks like Health Canada deal with this issue not too long ago and they did a ten year retrospective review looking at ADHD treatment in adolescents. They found in the past decade there was an aggressive stance to try to treat children with ADHD. By 10, in fact, 9 percent were treated with stimulants, and by 15, 4 percent of them were treated. During the decade they saw a 50 percent reduction in the suicide rate in the population studied.

So I think comments that were mentioned. I mean, it's similar to the black box warning with antidepressants, is it the drug or the illness that's causing the suicide? It looks like, in their data at least, they found that the black box warning wasn't really associated with the drug, but really the preexistent comorbid conditions.

DR. HUDAK: Dr. Davis?

DR. DAVIS: Thank you. I think what people are saying is it is complicated to go through these databases and try to figure out

causation versus association. I think the fact that you've gone through the cases and are able to eliminate, I do think that when the drug's stopped and there's no response that does say something. But, you know, when we're looking and you say, okay, there's 24 deaths over a three year period in kids 6 to 17, I'm not a psychiatrist, but it would make me nervous if a 6 year old somehow dies from this versus a 17 year old. So that part is hard to tell.

But I would think what you would have to do, and you have access to these data when the drug was approved, or other drugs in similar populations is be looking at the placebo group for background rates of what -- or published in the literature somehow in children like this who are being treated with other drugs. What are the background rates of mortality or suicide or anything else to see if this is normal background or not. I'm not sure if that's the best way to tease it out, but that would seem to make the most sense to me if you could do a real placebo control

trial. Prospective data is much more important than the retrospective analysis, and so if you can go to other databases of similar drugs and look at a variety of placebo groups and see if this makes sense, then I think that would reassure folks that this is the underlying disease process and not an association with the drug.

DR. HUDAK: Dr. White?

DR. WHITE: If you look at the New England Journal of medicine article in 2011 that we reviewed previously looking at cardiovascular risks. This is a large study that was done in several large databases. In Table 2, they have the characteristics of the cohort members who were taking ADHD medications versus a matched control group as best they could do in the database. The baseline previous suicide attempts in nonusers was 0.1 and in current users it was 0.3. I'm not quite sure how to interpret that, but this would suggest that there's a high risk pre-use of the medication for suicide within the population of children who will be taking these ADHD meds.

This is going to be an incredibly difficult study no matter how you set it up to figure out what is due to the medication and what's due to premorbid conditions or comorbid conditions. I don't know how you can separate it out. You certainly wouldn't be able to do a randomized study against placebo. This may be the best data that's available. It was a huge study. This is the best I could come up with. We did look at it about three years ago, I think.

DR. HUDAK: Doctor Turer?

DR. TURER: So I think the comments regarding the very select population that was studies in the randomized trials is really on point. It's notable, 95 percent were white, all the children had a BMI under 97th percentile, no hypertension, no psychiatric med use. They did do prospective assessment of suicidality and didn't see a signal, but there was a child that overdosed and showed aggressiveness in those trials. So, you know, I do wonder about the signal of aggressiveness, but then also, you know, what is

being done to improve the representation of the real population in these trials?

DR. HUDAK: Dr. Walker-Harding? Did you have a question?

DR. WALKER-HARDING: Okay. My question? So the thing I wanted to bring up too is when you look at the 52 it says suicidal, self-injurious, international overdoes. Suicide and self-injury are not necessarily the same thing, and many times in this group it is not. It's very common to see kids who are self-injuring that have nothing to do with suicide that are also ADHD diagnosed. And intentional overdose, I'm not sure if that's also the kids who are abusing the medication or not. It was not clear, but this is also a medication people abuse.

So, you know, that was unclear, but I do think that we can't say that all these 52 people are suicidal. That's actually not what's here. It could be, possibly, teased out further. But when you look and you see there were four suicides, you know, suicidal ideation, again, not

necessarily the same thing or even attempts. So, you know, when I look at this I'm not as -- it's not teased out. I'm not really clear what the 52 means. It's extremely rare to see an adolescent with ADHD that doesn't have a co-occurring disorder. So, I mean, it's really hard to tease that out.

Now, if you said to me that, you know, the 6 to 10 year olds are having suicidal, self-injurious, change in aggressive behavior, which also can be interpreted by people who have -- aggressive behavior can be seen by some people -- that could be a sign of the ADHD. It's how people actually define what they're seeing, what groups they're looking at. Some people get labeled as aggressive when maybe they're having depression or other kinds of issues. So, again, I think this is very, very difficult to tease out and say that somehow there is a suicidal increase. Nothing here to me stands out at all as an additional concern. The way it's written and the way it's looked at it would be impossible to tell.

DR. PORTMAN: This is Ron Portman. I think the issue here is that clinical trials in pediatrics, in particular, are designed as a partnership between the industry, the regulators, and act of omission to basically get as clear a picture as possible as to whether a drug works. Is it safe? Is it efficacious? It's not a real world situation where you're going to necessarily see how it's going to work in every situation. That's the issue, I think, that we face here.

DR. HUDAK: Dr. Cnaan?

DR. CNAAN: So one of the four cases of completed suicide was one week after the start of the drug, and two cases reported a positive dechallenge. So there were at least three cases out of the 52 that showed something. I guess I want to go back to the question that was at the beginning of this discussion. What is it that we have to see or the FDA has to see in order to make this issue a little more clear? And I do want to note that on the label in the section describing the studies it doesn't describe -- it describes

all the studies, but it doesn't describe that comorbid conditions were excluded. For that you actually need to go to the literature, so that if you're either a provider or a parent reading every single letter of the label you won't find anything more about this except in the use and abuse section.

DR. HUDAK: Okay. Does anybody have a recommendation to bring forward other than the FDA? Dr. Dracker?

DR. DRACKER: You know, this is so difficult because you don't know if treating a child with a comorbid condition with a stimulate increases the risk for suicidal behavior or decreases the risk, per say. To even say that you have to warn people that if a patient has a comorbid condition, using a stimulant may increase potential for it. We just don't have that data, except for that antecdotal data from Canada from University of Montreal which looks like good data. But I think in light of that, I think all we can recommend continued surveillance with more

attention in getting data should events come up.

DR. HUDAK: Dr. Havens?

DR. HAVENS: What kind of data would you recommend that they get to further clarify the issue? We heard before that GERD in children under a year of age isn't acid related, so the FDA felt comfortable saying don't use those stupid drugs in children under a year of age. Is there a body of evidence that could be brought to bear here that we could request of the FDA that would allow clarification of this specific question of use in the general population rather than use in a study population that would further allow a change in labeling or suggested use at the level of the FDA? That's what I think is a really complicated question.

DR. HUDAK: Doctor --

DR. DRACKER: I just want to answer his comment. Clinically speaking, if I have a 14 year old boy who's ten or four who has a history of -- I get a history of oppositional defiant disorder with ADHD diagnosed. I'm hesitant to put that kid

on Adderall, to be very honest with you. There's some clinical concerns you have when you see a patient who presents in a certain baseline manner that goes into your decision making as to what drug you might use.

So I think the clinicians' consideration as to what drug to use and what child might be at increased risk for suicide has to be part of the consideration. All I was suggesting is that getting some additional clinical information about an adverse outcome like suicide or homicide is important.

DR. HUDAK: Doctor White?

DR. WHITE: I'm going to go back to the New England Journal of Medicine article and say there's a database that exists that may have some of this data. It was used specifically to look at cardiovascular risk, but that data that was acquired does have some information about suicidality and ADHD medications. It might be that that databased could provide some additional information to help us answer this question.

DR. HUDAK: How many patients are in that study?

DR. WHITE: Hold on, hold on. Hold on. I'm slow. I'll get there. It's Wilson Cooper, 2011. It is a database cohort study, automated data from Tennessee Medicaid, Washington State Medicaid, Kaiser Permanente California, and Optimum Insight Epidemiology, 1,200,438 children and young adults between 2 and 24 years of age. 2,579,104 person years of follow up. So it was a massive, massive collection of data, and what you're looking for may be buried in this bit of data. If we could get access to it, it might be a place to look instead of going back and trying to reinvent the wheel.

DR. HUDAK: I think that's an excellent suggestion. I would just comment that I'm hearing what my colleagues around the table are proposing in terms of a clinical trial, randomizing patients who've got some comorbidities, but not others to sort of see an effect upon suicidality or aggression. That might require many, many, many

patients, and be very difficult, I think, to do. I think an approach such as this, looking at database with millions of patients and more millions of patient years to see if there is an effect identified might be reasonable.

Very good discussion. I have a hard time talking about alopecia after talking about suicidality, but in any case. The first question is whether or not FDA -- we support the FDA's recommendation for continuing ongoing surveillance, and let me be clear what a vote yes means with that. Would that mean that we would have this presented back to us in a couple years? Would that have to be added on to a motion?

DR. NELSON: You know, absent the specific identification of a concern and a question about the data that you would be interested in seeing, unless, although I suspect there would be another amphetamine coming to the PAC at some point due to a labeling change, this would not come back unless there was a PREA or BPCA stimulated labeling change.

But, I mean, I heard a lot of discussion but listening and letting it evolve I didn't hear a clear answer to the question as to whether there was a concern here or not. I mean, that was -- you know, I was waiting to see if I did, but I didn't. Particularly from those who've used these drugs a lot. But routine monitoring, we would continue to actively monitor the adverse events that are coming in, and we can certainly tell you what we think about alopecia. I agree that seems somewhat of a less important than the suicidality, but there'd be no particular report back unless there's another amphetamine that would be coming back for a labeling change at some point in the future.

DR. HUDAK: So just to follow up on Dr. White's suggestion, would it be possible for FDA to partner with the authors of this database to investigate more fully?

DR. NELSON: I have no idea about how that would be done operationally. It's a five year old database, and if it's Medicaid stuff it's

claims and things, and whether or not it was even maintained, I would have no idea whether that's doable from a practical perspective or not. I don't know if others would want to comment. Bob?

DR. LEVIN: It's possible because FDA did collaborate, to a certain extent, with the design and the analysis, so we could look into it.

DR. HUDAK: So we have, I think, three things to vote on here. The first is whether or not the committee agrees with FDA's recommendation to continue ongoing surveillance under the consequences outlined by Dr. Nelson, so we'll do that first. Alright. So we'll go around the room starting with Dr. Walker-Harding.

DR. WALKER-HARDING: Leslie Walker-Harding, concur.

DR. TURER: Christy Turer, concur.

DR. BAKER: Susan Baker, concur.

DR. KASKEL: Rick Kaskel, concur.

DR. MINK: Jon Mink, concur.

DR. CUNNINGHAM: Melody Cunningham, concur.

DR. HOEHN: Sarah Hoehn, concur.

DR. CATALETTO: Mary Cataletto.

DR. CAMPBELL: Jeff Campbell, concur.

DR. WHITE: Michael White, concur.

MS. CELENTO: Amy Celento, concur.

DR. HAVENS: Peter Havens, concur.

DR. RAKWOSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin, concur.

DR. DAVIS: Jon Davis, concur.

DR. MOON: Marc Moon, concur.

DR. DRACKER: Bob Dracker, concur.

DR. CNAAN: Avital Cnaan, concur.

DR. HUDAK: Okay. And if we can bring up the last slide once again, so I get this correct. So the second vote would be on the FDA to continue to investigate specifically signal for alopecia, and for that particular review to come back at a future PAC meeting. Okay. We'll go around the room starting with Dr. Cnaan.

DR. CNAAN: Avital Cnaan, concur.

DR. DRACKER: Bob Dracker. I concur. However, I think the distinction of whether it's

trichotillomania or not is important.

DR. MOON: Marc Moon, I concur.

DR. DAVIS: Jon Davis, concur.

DR. TOWBIN: Kenneth Towbin, concur.

DR. RAKOWSKY: Alex Rakowsky, concur with the caveat this will probably have to come back to the PAC if it's just a small change to the label.

DR. HAVENS: Peter Havens, concur.

DR. CELENTO: Amy Celento. I concur.

DR. WHITE: In my current state of recovery from acute alopecia, I concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. HOEHN: Geez. Well, I voted no because I didn't think it needed to come back if it was just a label change and it was alopecia which it sounds like other people agreed with. They just hit the yes button instead of the no button, but I hit the no button.

DR. CUNNINGHAM: Melody Cunningham, concur.

DR. MINK: Jon Mink. I concur.

DR. KASKEL: Rick Kaskel, concur.

DR. BAKER: Susan Baker, concur.

DR. TURER: Christy Turer. Only comment is alopecia can be connected to weight loss, so I'd just look at the weight, but I concur.

DR. WALKER-HARDING: Leslie Walker-Harding, concur. And I'd like to, again underscore making sure it's not trichotillomania and it's actually alopecia.

DR. HUDAK: Okay. So I'd just correct my colleague, Dr. White, that he does not suffer from alopecia. He suffers from acute hair volume loss. So the third -- all in a good cause, by the way. All in good cause.

DR. WHITE: Oh, yeah.

DR. HUDAK: So, okay.

DR. WHITE: (inaudible)is a great one.

DR. HUDAK: Exactly. He raised $1,500 for children. So the third motion here would be for the FDA to work with, specifically, their former partners in this study that was published

and, perhaps, other sources of information to try to do a deeper delve into the issue of suicidality and aggressiveness as a real cause and effect issues with this particular medication. So go around the room starting with Dr. Walker-Harding. Excuse me?

DR. DRACKER: Vote first.

DR. HUDAK: Oh, vote.

DR. DRACKER: You just (inaudible) though.

DR. HUDAK: Did I hit --

DR. DRACKER: You didn't ask them to push the button first.

DR. HUDAK: Oh, I'm sorry.

DR. DRACKER: We have to vote.

DR. HUDAK: Push your buttons first. Thank you. I had a moment there. Okay, so we'll go around from Dr. Walker-Harding and record our votes orally.

DR. WALKER-HARDING: Leslie Walker-Harding. I concurred. And also just if there are other studies please look for those with

a good level of diversity of people.

DR. TURER: Christy Turer, concur.

DR. BAKER: Susan Baker, concur.

DR. KASKEL: Rick Kaskel, concur.

DR. MINK: Jon Mink, concur.

DR. CUNNINGHAM: Melody Cunningham, concur.

DR. HOEHN: Sarah Hoehn, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. WHITE: Michael White, concur.

MS. CELENTO: Amy Celento. I concur.

DR. HAVENS: Peter Havens, concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin, concur.

DR. DAVIS: Jon Davis, concur.

DR. MOON: Marc Moon, concur.

DR. DRACKER: Bob Dracker, concur.

DR. CNAAN: Avital Cnaan, concur. And according to this paper it is a diverse cohort, so this might have the answers we're seeking.

DR. HUDAK: Very good. So I think we've

voted on all three resolutions and we will move to the next presentation unless somebody signals me otherwise. And that would be Dr. Khurana proceeding to talk about Symbyax. Is there anyone else from FDA who's joining the table for this? Yes. So we'll wait until they are in place and you can introduce yourselves and we'll proceed.

DR. SUGGS: Hi. I'm Courtney Suggs, safety evaluator with DPV.

DR. READY: Travis Ready, drug utilization DPV too.

DR. HUDAK: Thank you. Okay.

DR. KHURANA: Okay. Thank you. Next I'll be presenting the pediatric focused safety review for Symbyax. This is the outline for my presentation. Symbyax is a fixed combination of two psychotropic drugs, olanzapine an atypical antipsychotic and fluoxetine hydrochloride, a selective serotonin reuptake inhibitor or SSRI. Symbyax is approved for treatment of acute bipolar I depression in both adults and pediatric patients age 10 years and older, and for treatment

resistant depression only in adults.

Symbyax is July 2013 approval in patients 10 years to 17 years of age prompted the safety review. The pediatric approval was based on fulfillment of a PREA safety and efficacy study for treatment of bipolar depression. This PREA requirement was triggered following approval of a new dosage strength in 2007.

The next few slides will highlight relevant safety information in Symbyax labeling. The box warning for Symbyax is consistent with the class warning for all approved antidepressants, and warns of the increased risk of suicidal thoughts and behavior in children, adolescents, and young adults based on pooled analyses from short term placebo controlled trials. The box warning also states Symbyax is not approved for use in patients less than 10 years of age.

Labeling contraindications warn of the risk of serotonin syndrome with concomitant use of monoamine oxidants inhibitor, and the risk of QT prolongation of Symbyax's use concomitantly with

pimozide or thioridazine. The warnings and precautions section of Symbyax labeling contains 23 subsections which are listed over the next two slides with prominence given to the possibility of suicidal ideation and behavior. I'll be presenting the labeled adverse events from our safety review and the context of the relevant subsections from these two slides.

So as I mentioned, pediatric approval of Symbyax was based on results from a single trial. This was an eight week multi-center randomized double blind placebo controlled forced dose titration trial in 255 patients 10 years to 17 years of age with acute bipolar 1 depression. Results show the superiority of Symbyax over placebo for the primary efficacy endpoint. The types of adverse events observed were generally similar to those seen in adults. But when compared to adults and to placebo treated pediatric patients a greater proportion of Symbyax treated pediatric patients experienced weight gain and had increases in fasting lipid levels, hepatic

enzymes and prolactin levels.

The frequency of weight gain and magnitude and frequency of the laboratory changes were similar to those previously observed in placebo controlled olanzapine monotherapy studies in adolescents. A greater main increase in QT interval was also noted in Symbyax treated pediatric patients, but not to a level considered clinically meaningful. Information from the pediatric trial was added throughout Symbyax labeling. The pediatric use subsection specifies the recommended starting dose, which is lower than the initial dose recommended in adults. Flexible dosing is recommended rather than the force dose titration used in the efficacy trial.

The pediatric use subsection also cross references to key safety sections of labeling. The individual components of Symbyax have each been previously studied in pediatric patients, and the combination showed no evidence of an increased safety risk to warrant revisions to labeling contraindications or to warnings and precautions

at the time of pediatric approval.

This figure shows the number of pediatric patients less than 17 years of age who received dispensed prescriptions for combination olanzapine fluoxetine drug products from U.S. Outpatient retail pharmacies from July 2010 to June 2015. As you can see, the nationally estimated number of pediatric patients who received a dispensed prescription during the 12 month period ending in June 2011 was approximately 1,500. This number decreased each subsequent year to approximately 500 patients during the 12 month period ending in June 2015. Notably, use in the unapproved pediatric population, less than 10 years of age, was low and remained stable throughout the examined time period.

During the same time period, psychiatry was the top prescribing specialty followed by family practitioners while pediatric specialists accounted for less than 1 percent. According to an office-based physician survey database there were no diagnosis reported in association with the

use of combination olanzapine fluoxetine drug products in pediatric patients during the same time period.

Now, we'll look at the pediatric focused adverse events. We identified 22 pediatric adverse events between June 30, 2015 and the 2004 initial marketing availability of Symbyax. We reviewed all the reports and excluded three duplicate reports of a fatal case, resulting in the selection of 19 cases which were the basis for this pediatric focused safety review. These included one fatal report and 18 non-fatal reports, including one report of transplacental exposure.

So our review identified 18 serious labeled adverse events, including the single fatal report. These labeled events are well-characterized, and the majority are listed in different subsections of labeling warnings and precautions as noted in this slide. There were a handful of other labeled events related to weight gain, allergy, tardive dyskinesia and dystonia.

One case reported breathing problems in a premature neonate requiring sufactant administration, but the narrative had insufficient details for us to determine that transplacental Symbyax exposure had occurred.

The single fatal case described a completed suicide in a 7 year old boy with an extensive medical and psychosocial history whose behavior had already been deteriorating before he started Symbyax therapy. His underlying psychosocial conditions and concomitant psychotropic drug use prevented us from being able to determine whether or not his death was Symbyax related. Notably, this patient was 7 years old. The box warning and labeling warnings and precautions state that Symbyax is not approved for use in treating any indications in patients less than 10 years of age.

One case of trans-placental exposure was reported in a full term male born to a mother who had taken fluoxetine and Symbyax for an unspecified duration at an unknown time during her

pregnancy. He was cyanotic at birth, required intubation for respiratory distress, and was subsequently diagnosed with transposition of the great vessels. Congenital cardiac anomalies are not listed as a complication of trans-placental exposure to Symbyax in product labeling, and there was not enough information in the narrative for us to assess causality in this case.

Symbyax labeling does state that respiratory complications requiring respiratory support have developed in neonates exposed to fluoxetine and other SSRIs late in the third trimester. But this case did not specify how long the mother had used fluoxetine and Symbyax while pregnant and when she used these drugs during her pregnancy.

This concludes the pediatric focus safety review for Symbyax. We identified no new pediatric safety signals. We recommend continuing ongoing surveillance. Does the committee concur? Again, I would just like to thank everyone on this slide for their help with this presentation.

DR. HUDAK: Thank you. If you'd like to sit down you can sit down.

DR. KHURANA: Yes. Thank you.

DR. HUDAK: Dr. Mink?

DR. MINK: Well, there's good news. And that is that fewer people are prescribing this for children, and it seems to be falling off. It's one of the few situations that this committee reviews where there's actually decreasing use rather than increasing use following a change in labeling. Does anyone know -- the striking thing to me was that pediatricians aren't prescribing this, but family practitioners are. Is there any way to know from the data whether they're initiating treatment with this or whether it's being initiated by someone else and they're prescribing the refills?

DR. READY: It's not one of the standard reviews that we do for one of these PAC meetings. We generally have the ability to do some ad hoc further analyses.

DR. MINK: I'm just curious because I

think, you know, a fixed ratio combination medication like this is -- maybe for stable maintenance once you do a titration, but it also is a real convenience, so it's easy to write a prescription for one thing and say, hey, look at this. Again, I just wonder how much of the -- I'm not concerned about new safety signals, but of the things that are known how often that happens because of a prescription that's really more for convenience rather than well thought out, as we have been talking about all day long.

DR. HUDAK: Dr. Hoehn?

DR. HOEHN: I had the exact same thought when I was reviewing this data in preparation for the meeting which was why -- because to me, bipolar is a rare -- it's not a typical diagnosis for a pediatrician to make, and that's why when I went through it I had the same exact question which is if it's a new prescription or initiation of a new medication if it should be restricted to psychiatrists initiating it under a certain age. I mean, as a pediatrician it doesn't seem like

diagnosing bipolar is a typical thing for a pediatrician to do, and that's why I was also interested in the fact that both family practice, and I think nurse practitioners, prescribe it frequently. It's one thing if you can't get in to see a psychiatrist again, but if there is some way to track who initiated the start of the prescription.

DR. HUDAK: Is there an answer for that? Probably?

DR. LEVIN: I think it would probably be difficult to determine definitively. I think as Dr. Mink suggested, this is speculation, but it might be likely that a fair proportion is being started inpatient facility, perhaps, maybe at least a portion of that. I think we'd have to look at Medicaid data or other outpatient data. We could try. I think it will be difficult to track that and try to put all the data together.

DR. HUDAK: Dr. Dracker?

DR. DRACKER: Dr. Mink, I'm glad you said that because I am very hesitant to make that

diagnosis of bipolar disease which is still contentious, even from the psychiatric standpoint as to what age you can diagnose bipolar disease in children. But I would never -- when I saw that drug on the list for today's discussion I said, my god, I would never prescribe a combination medication in a kid. I don't even like using a polypharmacy in children, let alone a combination medication.

The one thing I can tell you though is sometimes we get representatives, pharmaceutical representatives coming in with these new combination drugs, and pediatricians, in general, are very hesitant to listen to what we're told and to just try things out on children. That may be a cultural difference in how we practice.

DR. HUDAK: Dr. White?

DR. WHITE: We've noticed similar prescriptive practices in the past where family practitioners are much more likely to give drugs for various and sundry psychiatric disorders. And it would be interesting to see if there's a

geographical pattern to that. In Louisiana we don't have anywhere near enough psychiatrists to take care of all the kids that we have with psychiatric disorders. And in particular, the rural areas are more likely to be covered by family practitioners than they are by pediatricians or psychiatrists. So you might find some useful information there to help you with what those practices might be.

DR. HUDAK: Dr. Davis?

DR. DAVIS: In our area the pediatricians will tell you that 50 percent of all their visits total in their offices are now behavioral related pediatrics, and more and more of them are bringing in psychologists because they just can't keep up with them and then don't feel they have the training to be able to do that.

DR. HUDAK: Dr. Nelson?

DR. NELSON: Just as a quick comment. It, of course, would be interesting to answer some of these questions about geography and prescription patterns, but it strikes me it's a

bit outside of the FDA purview.

DR. WHITE: It wasn't a suggestion.

DR. NELSON: Okay. Because it's not clear to me how we would then take that and translate it into labeling and the like, so I just wanted to make that point. We don't regulate medical practice. This is a label that we thought would help.

DR. HOEHN: I think that was my question though. Is I didn't know if you could put on the label recommend initiation of prescription limited to psychiatry? I didn't know if that could factor into the labeling?

DR. NELSON: Well, as you well know the controversy over even doing that for propofol, you know, which then resulted in a lot of kerfuffle between anesthesiologist pediatric critical care, and the emergency room physicians. I'm not sure that outside of that sort of monitored anesthetic care there's a lot of precedent to try and restrict labeling to licensed physicians of one class versus another, but.

DR. HUDAK: Dr. Towbin?

DR. TOWBIN: Just a couple of thoughts about this. One is there aren't nearly enough child and adolescent psychiatrists if one were to kind of take that step it would, I think, be quite unfortunate in so many ways. Even that being said, the entity of pediatric bipolar disorder is really in kind of a transition because for a long period of time children with hyperarousal symptoms like ADHD and irritability were given the diagnosis of bipolar disorder in the absence of episodes that general psychiatrists would generally regard and should regard as the sine qua non for that diagnosis. So some of these individuals that were diagnosed with bipolar disorder actually had chronic irritability and ADHD symptoms.

I think the other comment is that olanzapine, in particular, is a drug that is very tightly associated with weight gain, even among the second generation antipsychotics. I'm hoping, as Dr. Mink pointed out, that the decline in the

use of this drug is closely associated with people thinking that olanzapine is not anybody's go-to-agent for problems where antipsychotic is necessary. It's been pretty clear from research done with psychosis in children that this might be a preferred second line drug, at least in the field right now. The side-effect profile kind of renders it into a different category.

DR. HUDAK: Okay. I think we can call the question about FDA recommending continuing ongoing surveillance, so please vote. Alright. We'll go around the room starting with Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. MOON: Marc Moon. I concur.

DR. DAVIS: Jon Davis, concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. HAVENS: Peter Havens, concur.

MS. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White, concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. MINK: Jon Mink. I concur.

DR. KASKEL: Rick Kaskel. I concur.

DR. BAKER: Susan Baker. I concur.

DR. TURER: Christy Turer. I concur.

DR. WALKER-HARDING: Leslie Walker-Harding. I concur.

DR. HUDAK: Thank you. Okay. So should we power through the next two? It might make the discussion more concise. Alright. So we will do that. Dr. Snyder, who is from the Division of Pediatric Maternal Health, Office of New Drugs in CDER will speak first about Seroquel and Seroquel XR. While we're having the comings and goings. There is at least one new person who is sitting down. If you could introduce yourself.

DR. CHAN: Vicky Chan, safety evaluator, division of pharmacovigilance.

DR. HUDAK: Thank you. Okay.

DR. SNYDER: Alright. Thanks. So I'm presenting the pediatric focused safety review for Seroquel and Seroquel XR or quetiapine fumarate. By now you all are familiar with this outline for our presentations today. So Seroquel and Seroquel XR is an atypical antipsychotic originally approved on September 26, 1997. Pediatric labeling changes occurred on December 2, 2009 and April 30, 2013. The April 2013 labeling change initiated this pediatric advisory committee presentation today. There are currently no post-marketing requirements for this product.

Both Seroquel and Seroquel XR are indicated for the treatment of schizophrenia in patients 13 years of age and older and for bipolar disorder with depressive episodes in adults. Seroquel is approved for the treatment of manic bipolar episodes in patients 10 years of age and older, and Seroquel XR is approved for the treatment of manic and mixed bipolar episodes in patients 10 years of age and older, and major

depressive disorder in adults.

Three pediatric studies have been completed in pediatric patients. The labeling change resulting from the last study on bipolar depression initiated the current PAC review. In this study the safety and efficacy of Seroquel and Seroquel XR in the treatment of bipolar depression was not established in children and adolescents aged 10 to 17 years of age.

Now we'll move on to labeling. Seroquel and Seroquel XR contain a box warning. The aspects of this box warning that is relevant to pediatric patients is a risk of increased suicidal thoughts and behaviors in pediatric patients taking antidepressants. The entire box warning is included for your reference here.

Since the product is indicated for treatment of pediatric patients 13 years of age and older with schizophrenia and patients 10 years of age and older for bipolar disorder, information regarding the use for the approved pediatric indications are sprinkled throughout labeling.

This slide includes the dosing in the appropriate pediatric populations.

This slide includes the warning and precautions for the product. With the exception of dementia related psychosis and stroke, all may be relevant to the pediatric population. Warnings and precautions are continued on this slide. All of these are potentially relevant to the pediatric population. This slide includes the common adverse reactions seen in clinical trials and as part of the post-marketing experience. This slide includes the pediatric use subsection and the use in specific population section of labeling which contains information regarding the basis of pediatric approval. The clinical pharmacology and clinical studies sections also include the pertinent pediatric study information that supported approval.

Now we'll move on to pediatric use. Approximately 2.8 million patients received a dispensed prescription for quetiapine and quetiapine XR from U.S. outpatient retail

pharmacies from August 2014 through July 2015. Pediatric patients aged 0 to 17 years accounted for about 7 percent or 184,000 patients, while patients aged 17 years of age and older accounted for approximately 93 percent of total patients.

This slide compares use in pediatric patients 0 to years and 9 to 17 years of age over the four year time period from August 2011 to July 2015. Approximately 90 percent of the use in the pediatric population occurs in pediatric patients 10 to 17 years of age. Again, for the review period from August 2011 to July 2015 psychiatry was the top prescribing specialty with approximately 47 percent of the total numbers of dispensed prescriptions. Pediatric specialists accounted for less than 1 percent of total prescriptions. The primary diagnosis captured in pediatric patients 0 to 9 years of age was attention deficit disorder, and for pediatric patients 10 to 17 the primary diagnosis was effective psychosis.

Now we'll move on to the cases selected

for review from the FAERS database. This table includes the adverse event reports submitted from the time of the last PAC review until the end of July 2015. There are nearly 20,000 reports. Of the 20,000 reports, 838 were pediatric, 670 of those reported to be serious. There were 77 pediatric deaths. Of the 670 serious pediatric reports identified, 592 were excluded, leaving 78 pediatric case reports with 16 deaths. The reason for the 592 excluded reports are included on the next slide. Duplication of cases was the primary reason for exclusion for transplacental trans-mammary exposure, and labeled events being the next two larger categories. Other categories were minor contributors given the overall number of cases.

The Office of Pediatric Therapeutics reviewed the unlabeled cases due to transplacental exposure and no specific patterns of anomalies was noted in FAERS. But given the broad spectrum of anomalies noted, and the widespread use of Seroquel and Seroquel XR, the FAERS reports do not

suggest a new clinical signal of concern.

This slide includes the characteristics of the 78 pediatric cases identified for review. The majority of the cases occurred in patients 12 years of age and older with only five cases below 6 years of age. Males slightly outnumbered females, and there were more U.S. cases compared to foreign cases. The characteristics of the 78 pediatric cases are continued on this slide. Bipolar disorder was the largest single reason reported for use, 29 patients were hospitalized with the event.

This slide lists the reported patients that died. Patients ranged in age from 4 to 16 years with a median age of 14 years. Half of these cases were from literature. Thirteen cases reported multiple concomitant drug ingestion, and these cases were otherwise non-interpretable in terms of causation. Three cases were interpretable and are discussed on the next slide. Three cases of death reported quetiapine is the only drug case. The first case was a 15 year old

female patient who died after ingesting two quetiapine tablets of unknown strength. No past medical history of concomitant medications were reported for this patient. In the emergency room the patient's heart rate was elevated to 150 beats per minute. Once her heart rate was stabilized the patient was transferred to an inpatient psychiatry unit. Six hours later the patient returned to the emergency room seizing with fixed and dilated pupils. Cardiopulmonary resuscitation failed and the patient died. No cause of death was reported.

The second case was a 15 year old male patient with bipolar disorder who died in sepsis. The duration of treatment with quetiapine was not specified, and according to the report, neuroleptic malignant syndrome was ruled out. Past medical history, concomitant medications, and cause of death were not reported. The last case was a 14 year old female patient who died after a potential exposure to quetiapine. Concomitant medications, dose of quetiapine, and cause of

death were not reported.

Now we'll move on to the unlabeled adverse events. On this slide, the categories for unlabeled events and number of events are listed. We'll go through these individually on the next few slides. Throughout the slides, the individual unlabeled event will be underlined. There were 28 cases reported under the category of psychiatric disorders, suicidal thoughts and behaviors. As previously noted, labeling for Seroquel and Seroquel XR contains a box warning for suicidal thoughts and behaviors. The reasons for taking quetiapine are listed on this slide. Some of these patients were taking quetiapine for unlabeled indications. Several of the patients were on concomitant medications that may have contributed to the event.

There were seven cases reported under the category of other psychiatric disorders. Four cases did not report an outcome. Three cases reported resolution when quetiapine was stopped, and two of the patients reported reocurrence when

quetiapine was reintroduced. One of these cases noted resolution of tics with lowering the dose, but later reported that the tics resolved once haloperidol was added despite increasing the dose of quetiapine.

There were seven cases reported under the category of eye disorder. Outcome is not reported in four of the seven cases. One case of a patient with papilledema. This patient was also on fluoxetine which is labeled for optic neuritis. Miosis was reported in a 10 month old patient after accidental ingestion of 50 milligrams of quetiapine and 25 milligrams of an unspecified antidepressant. There were six cases reported under the category of GI and hepatic disorders. The severity of hepatic enzymes increase could not be assessed since actual transaminase values were not provided. The case of hepatic steatosis was confounded by metabolic syndrome and concomitant use of fluoxetine which is labeled for hepatic failure and necrosis and hepatitis. The cases of GERD and paralytic ileus did not report an

outcome. Half of the case reports were related to underlying disorders.

There were four cases reported under the category of pulmonary, respiratory, and vascular disorders. The case of pulmonary embolism was complicated by concomitant use of medications, including enoxaparin, an antithrombotic agent. In three of the four cases an event outcome was not reported. One patient on lithium and quetiapine developed a pleural effusion associated with lithium toxicity and acute kidney injury, but did make a full recovery.

There were four cases reported under the category of nervous system disorders. Two patients were reported with loss of consciousness or as passed out. But quetiapine is labeled for sedation and drowsiness. None of the cases reported the dose of quetiapine, the action taken, or an event outcome. There were two cases reported under the category of musculoskeletal disorders. The first case was a female patient aged 15 who reported sedation, muscle spasm, and

inability to move after taking an incorrect dose of quetiapine. The event resolved after quetiapine was discontinued. The second case occurred in a male patient who complained of incontinence, muscular weakness, paresthesia, and visual impairment while on both sertraline and quetiapine for an unspecified indication. The event outcome was not reported. Of note, muscular skeletal stiffness and paresthesia are both labeled events under the adverse reaction section of quetiapine labeling.

There were five cases reported under the category of miscellaneous disorders. There was a 16 year old patient with alopecia who reported hair loss seven weeks after starting both Seroquel at 75 milligrams three weeks after starting quetiapine at 50 milligrams. Quetiapine was stopped, but Seroquel was continued, and no other therapy for alopecia was given. No further hair loss was reported. A second case in a 12 year old patient with ADHD reported ventricular tachycardia when quetiapine XR was titrated from 50 milligrams

to 200 milligrams. The event resolved the same day and quetiapine was discontinued nine days later. In the remaining three patients quetiapine was continued despite the reported events.

So this concludes the pediatric focused safety review of FAERS reports. No new safety signal was identified. FDA recommends continued routine monitoring, and does the committee concur? Thanks to all the people on this slide for their help with this presentation.

DR. HUDAK: Okay. This is open for discussion. Dr. Hoehn?

DR. HOEHN: I have the same question/comment on this one as I did on the last one, which is just if there's any mechanism to at least encourage people that the initial treatment for something like pediatric schizophrenia should go through psychiatry. This one I think 44 percent of them were nurse practitioners who may be working in partnership with psychiatrists or may not be. But it just seems concerning that there's so many people using it for what should be

very, very limited indications in terms of what it's approved for.

DR. HUDAK: I was also concerned about use of the age group less than 2 years of age. It's hard to conceive how that might be. Maybe someone could help me out with that, but it's hard to conceive how that would be done or why that would be done.

DR. HOEHN: I thought those were unintentional. Were those prescribed to children less than 2?

DR. CHAN: The 10 month old was an accidental ingestion.

DR. HUDAK: Dr. Mink?

DR. MINK: I was just going to speculate, do these distinguish between prescribed versus un-prescribed use?

DR. CHAN: This includes both.

DR. MINK: This is both?

DR. CHAN: Yes.

DR. MINK: Do you make a distinction?

DR. CHAN: We can't specifically select

for prescribed use, so we collect all of them and we evaluate them on individual cases.

DR. MOON: It's Marc Moon. I suspect there may be some desperation use in Asperger's or autism.

DR. HUDAK: Dr. White?

DR. WHITE: There were ten diagnoses of infantile autism in the under 9 year old group which includes the ones you're asking about, so I assume that may have been the reason.

DR. HUDAK: Dr. Towbin, your wise words.

DR. TOWBIN: Well, I don't know if I have any real wisdom here. I guess there were a couple of comments that I might make. It's clear in the briefing materials and the slide that was posted didn't make this quite as clear, but this drug is approved for acute mania in children, and the trial that was done was a three week mono-therapy active agent versus placebo. What we see quite often is that these drugs are started and then continued for quite a long time. The side effect profile, the risks of this drug,

particularly metabolic syndrome increase with the duration of the drug. And so I think the idea that one might use a drug like this during an acute manic episode is one thing, but I think they're continued for a long time.

I think the second comment is a bit of redundancy with my earlier one which is the diagnosis of pediatric bipolar disorder is used in different ways in different places. There was a period of time when chronic irritability along with hyperarousal symptoms was called bipolar disorder, removing the criterion for an episode being essential, and so children with chronic irritability and hyperarousal symptoms would be given these agents, and given the diagnosis of bipolar disorder. I think we now know that that entity of chronic irritability and ADHD like symptoms is not the same as acute mania. It has a different course. It has different risk factors. And, in fact, one might treat it in very different ways instead of beginning with atypical and psychotics and mood stabilizers.

I think this is coming into more common view. My hope is that it will become more widespread over time. But the data that we are looking at, going back now some years, would still be in that time when individuals looked at chronic irritability as the same thing as bipolar disorder.

DR. HUDAK: Dr. Turer?

DR. TURER: I wonder if there is a role for a labeling change regarding the findings from this study. Noting that in bipolar with depressive features there does not appear to be efficacy. The other thing that's remarkable is that the number one diagnosis associated with a prescription for this in children, I think up to 9, was attention deficit. So would it bear labeling to state there are no data to support use of this in attention deficit syndrome?

DR. LEVIN: On the second point, as you note, there is a large proportion of pediatric patients whose diagnosis, with the data we have, is ADHD. This goes back to the earlier discussion

with Vyvanse. There's a tremendous amount of comorbidity with patients with ADHD, and probably at least 30 percent of these patients have conduct disorder or some severe behavioral disorder or just frank agitation, aggression, and violence.

So there's a fair amount of literature suggesting that many clinicians do use these drugs as a last resort to treat not the ADHD primarily, not the inattention or the primary. But it does treat impulsivity, but people seem to be targeting the more severe aggression and self-injurious or injury to others both intentional and unintentional. It's usually impulsive aggression rather than true intentional aggression. But that's a fair amount of use in that population and people clearly say they use it very carefully, but as a last resort. Even some practice guidelines, including in Canada, people do recommend, even though it's not approved, there are clinical guidelines suggesting that these drugs have a role for severe agitation and aggression.

In your first point I think we do -- as

far as labeling the study, if it hasn't already we typically include the negative result, both positive and negative results in labeling of the studies that have triggered the discussion. We can check on that. I can let you know if we already have that in labeling.

DR. HUDAK: Dr. Kaskel?

DR. KASKEL: Rick Kaskel. Do we have any numbers on how many patients are on lithium as well as this agent in a database?

DR. CHAN: We didn't look at that specifically, that combination specifically.

DR. KASKEL: It might be worth looking at. Lithium is an aflatoxin and you have a case here of one patient in acute renal failure.

DR. LEVIN: We have some capability of doing a concomitant medication analysis. It's somewhat limited, but we can occasionally get some information about that.

DR. HUDAK: Dr. Towbin?

DR. TOWBIN: Just one other thing to say. There is quite an interesting paper that Dr.

Olson published at the end of the year last year looking at the second generation anti-psychotics as a class in this population of children with irritability and aggression. What it shows is that the use sort of -- if you do this look by age. This is from a very large database of outpatient claims. To look the rate of this drug being used in males between 9 and 14 or 15 is where things really peak, and then after 15 it begins to come down again. Speaking to how often these drugs really are used to treat impulsive aggression, irritability kinds of behaviors. So I think it's being used largely as sedation for those kinds of events or to kind of keep a lid on those events. I think that's unfortunate.

I think the other part of that paper that was so interesting is how few of those individuals had any psychosocial intervention. The pharmacologic intervention was the only thing they were receiving. And, in fact, a very high proportion of those individuals had no diagnosis associated with the use of the medicine. What you

see, I think too commonly, are individuals who come from disadvantaged backgrounds, may have post-traumatic stress disorder, maybe in the foster care system, have a lot of aggression, have a lot of irritability and end up on these agents. I'm not saying everyone to a person is in that characterization, but I just think that these drugs are being used in ways that isn't a, if you will, eloquent, combined, thoughtful interdisciplinary approach to a very complicated problem.

DR. LEVIN: Dr. Turer, yeah, the labeling does include a description of this study that did not demonstrate efficacy as well as some efficacy and safety data. That's what we typically do with all pediatric studies. Was that your question about whether the study's described?

DR. TURER: Yes. Making it very clear that there was no evidence of efficacy for that specific indication.

DR. LEVIN: Right. Yes, it does.

DR. READY: Could I have Slide 15 up,

please? I just want to add the caveat, the very last line. These were very low numbers. Even with ADHD at the highest use mention they're extremely low, and so we don't generally like to generalize to the U.S. population. So I just want to make that call out.

DR. HUDAK: Any other thoughts before we vote? Put the question back up. Last slide. Hearing none we'll vote on the question of recommendation for continued monitoring for Seroquel and Seroquel XR. We'll go around the room from Dr. Walker-Harding.

DR. WALKER-HARDING: Leslie Walker-Harding, concur.

DR. TURER: Christy Turer, concur.

DR. BAKER: Susan Baker, concur.

DR. KASKEL: Rick Kaskel, concur.

DR. MINK: Jon Mink, concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. CAMPBELL: Jeff Campbell, concur.

DR. WHITE: Michael White, concur.

MS. CELENTO: Amy Celento, concur.

DR. HAVENS: Peter Havens, concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. DAVIS: Jon Davis, concur.

DR. MOON: Marc Moon. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. CNAAN: Avital Cnaan, concur.

DR. HUDAK: Very good, so that's unanimous consensus to continue monitoring for Seroquel and Seroquel XR. Alright. The last presentation for the day for drugs is done also by Dr. Snyder on SABRIL. Let me see if somebody is coming to the table specifically for this. It appears so.

DR. NELSON: While people are settling in let me just make one comment. You may have noticed in that last review that we had a review of the transplacental exposure cases. I just wanted to call your attention to that. We plan to

look at those in our planning meetings. One of the advantages of now having a neonatologist is we can do that, and we also have a maternal team that looks at that as well. So whether that comes back to the PAC, if we seek signals to go through, I mean, I just want to alert you that you may have noticed that, but you may not have realized that that was relatively new.

DR. HUDAK: Thank you, Dr. Nelson. Okay. So we have a bevy of people who've come to the table. If you could introduce yourselves so we could get started with the presentation. Thank you.

DR. STOJANOVIC: Danijela Stojanovic, DPV safety evaluator.

DR. KULICK: Corrinne Kulick, team leader, division of pharmacovigilance.

DR. HERSHKOWITZ: I'm Norm Hershkowitz, medical officer team leader, DNP.

DR. SHERIDAN: Phillip Sheridan, Medical reviewer, DNP.

DR. LEE: Joann Lee, drug use analysis,

from division of epidemiology.

DR. SNYDER: You ready? Okay, great. Alright. So I'm presenting the pediatric focused safety review for SABRIL or vigabatrin. Here's our ever present outline for the presentations today. Hopefully the last time you'll see it from us. Alright. So SABRIL is an anti-epileptic medication originally approved on August 21, 2009. The pediatric labeling change initiated these pediatric advisory committee presentation today occurred on October 26, 2013. There are no post-marketing requirements under the Pediatric Research and Equity Act or PREA, but there is currently a registry in place under a risk evaluation and mitigation strategy or REMS to evaluate potential visual loss with use of the product.

SABRIL is indicated for the treatment of refractory complex partial seizures or CPS in patients 10 years of age and older who have responded inadequately to several alternative treatments and as monotherapy for infantile spasms

in infants one month to two years of age. Pediatric studies were conducted in response to a Written Request. Those two studies are listed here. Exclusivity was granted in October 2013. These studies also fulfilled requirements under PREA.

Now we move on to labeling. SABRIL contains a box warning. Use of SABRIL has been associated with vision loss, and the product is only available under a REMS program. Since the product is indicated for treatment of pediatric patients 10 years of age and older with complex partial seizures (CPS) with an inadequate response to several alternative treatments and in infants one month to two years of age with infantile spasms, information regarding the use for the approved pediatric indication is sprinkled throughout labeling. This slide includes the dosing in the appropriate pediatric populations.

This slide includes the warnings and precautions in labeling for this product. The pediatric use subsection of the use in specific

population sections contains the information regarding the basis of pediatric approval. Of note, abnormal MRI changes have been observed in infants. The clinical pharmacology and clinical studies section also include the pertinent pediatric study information that supported approval.

Now we move on to pediatric use. Approximately 4,300 patients received a dispensed prescription for vigabatrin from U.S. mail order pharmacies during the recent 12 month period ending in July 2015. Pediatric patients aged 0 to 16 accounted for the majority at 81 percent or 3,500 patients. Over two-thirds of vigabatrin use was in children less than 6 years of age, while patients aged 17 years and older accounted for approximately 18 percent of total patients.

This graph displays the total number of pediatric patients who received a dispensed prescription for vigabatrin from U.S. mail order pharmacies stratified by age. The total number of patients receiving vigabatrin increased from 1,900

patients in the 12 month period ending in July 2013 to 3,500 patients during the 12 month period ending in July 2015. Of note, no sales were captured as distributed to retail pharmacies. Pharmacies that dispense vigabatrin as specially certified by the sponsor under the REMS program.

I think I skipped this one. Neurology was the top prescribing specialty for vigabatrin and accounted for approximately 77 percent of total vigabatrin prescriptions dispensed. The pediatric specialty group accounted for approximately 9 percent. No diagnosis data was associated with the use of vigabatrin in pediatric patients aged 0 to 16 years as of -- we reviewed the U.S. Office Base Physician Survey Data Database.

Now we'll move on to the cases selected for review from the FAERS database. This table includes the adverse events reports submitted from August 2013 to July 2015. There were 429 adult reports and 1,305 pediatric reports. Of the 1,305 pediatric reports there were 165 deaths with

majority reported in the U.S. We will be focusing on the U.S. reports in this review.

As previously mentioned, we're focusing on review of the U.S. deaths from August 2013 to July 2014 and the four events of special interest here. For the events of special interest the review window was expanded to include all cases reported from the date of approval. This slide includes the characteristics of the death cases separated by use and treatment of infantile spasms or seizures and epilepsy. The majority of cases occurred in patients treated for infantile spasms. I'll give you a minute to look at this slide.

This slide includes the characteristics of the death cases including age, sex, total daily dose, and reasons for use. The characteristics of the death cases are continued on this slide to include time to death and cause of death by system, organ, class. This slide contains an overall summary of the review of the death cases. In nearly 70 percent of the cases the cause of death was not known, and in most cases the details

surrounding the death were not well-characterized. As a result, there was insufficient information to assess causality.

When reported, the cause of death included respiratory, cardiac, and neurologic events. These causes of death were consistent with a natural history and poor prognosis of the underlying disorders in these patients. Additionally, most cases describe disease progression, infection, respiratory insufficiency, and underlying congenital disorders as possible contributory factors. In cases where weight was reported, vigabatrin was dosed appropriately.

Now we move on to discuss the events of special interests which are blindness, abnormal MRI, renal events, and pancreatitis. Blindness was identified in 28 cases. Although vision loss is identified in labeling, blindness was reviewed as a possible event of higher severity. The majority of cases occurred in patients with infantile spasms. Eighteen of the cases had insufficient information to assess the event. The

remaining eight cases are described on the next slide.

This slide includes the eight cases that had adequate details to review a report of progression of visual loss. There were a variety of comorbid conditions and concomitant medications that may have affected the association, but the role of vigabatrin could not be ruled out. On review, the visual changes noted in these patients included renal toxicity or visual field loss. This is consistent with vigabatrin labeling.

The second event of special interest is abnormal MRI. Labeling includes a warning and precaution that abnormal MRI changes have been reported in infants. Details from 22 of the cases are outlines on this slide. These cases were either uninterpretable or coincident with changes associated with WEST syndrome.

This slide discusses five cases where the MRI improved or normalized after vigabatrin discontinuation. In cases where there were adequate details for assessment, the MRI changes

were consistent with labeling or with the underlying condition.

The third event of special interest are renal events. Of the eight cases, five had sufficient information review. All these cases and underlying conditions that may have affected causality, although the contribution of vigabatrin to renal impairment could not be ruled out.

The last event of special interest in pancreatitis. Of the five cases, three contained sufficient information for assessment. Use of ketogenic diet as part of treatment and concomitant medications could have contributed to the events. However, a role of vigabatrin on contributing to the events cannot be ruled out.

This concludes the pediatric focused safety review of FAERS reports. Case reports with an outcome of death described disease progression in a population with underlying disorders and conditions, having a poor prognosis, and could be expected. Vigabatrin was not determined to be a causative factor. Cases of visual loss and MRI

changes in infants were consistent with the warnings and precautions in labeling. No new safety signals were identified. FDA recommends continued, routine monitoring. Does the committee concur? Thanks to all the people on this slide for their help with this presentation.

DR. HUDAK: Thank you, Dr. Snyder. You can sit down and relieve yourself if you'd like.

DR. SNYDER: Thank you.

DR. HUDAK: We're open for discussion. Yes?

DR. RAKOWSKY: So as part of the risk management plan is reporting of SAEs mandated or more encouraged because there's a huge amount of SAEs considering the number of patients who are obtaining this drug? There's like 1,000 SAEs for 3,000.

DR. LEVIN: Yes. In general, the regulations sponsor are required to report all serious adverse events.

DR. HUDAK: Dr. Davis?

DR. DAVIS: I think that's, in part,

because of the population you're dealing with. I mean, if these babies have infantile spasms these are, you know, children with the worst neurologic prognosis and outcome that are going to have multisystem organ involvement and things of that nature.

DR. HUDAK: Yes, Dr. Mink?

DR. MINK: Yes, these are the sickest of the sick. And I think really the outcomes are almost certainly more determined by their underlying disorder and other treatments of those disorders. But we don't know, it's a small number. My only question is with continued routine monitoring the surveillance that's in place by the sponsor and the requirement to have period eye exams, etcetera that would continue. That's completely separate from the post-marketing surveillance. Is that correct?

DR. STOJANOVIC: That is correct. It's part of the REMS program.

DR. MINK: Okay.

DR. HERSHKOWITZ: I'm sorry, my hearing

is not very good. The REMS is principally targeted at the monitoring of the visual events. At the present there's a special ophthalmological form. They also, of course, monitor seizure events as well because there has to be confirmation that the patient needs it and is being helped by it.

DR. HUDAK: Dr. Hoehn?

DR. HOEHN: I just want to second what was already said which is that, to me, almost all of this is just progression of underlying disease, MRI changes, all the respiratory deaths and things like that are what you would expect with or without treatment.

DR. HUDAK: Dr. Davis?

DR. DAVIS: I have to admit I'm fascinated by the MRI changes that occur. We could all say it's related to the underlying injury because that's what they're being treated for, but the fact that some of them went away when the drug was stopped I find fascinating. Any thoughts about what that might be or what that

would represent?

DR. SHERIDAN: I think the result of the changes that you're referring to were the ones that were first described by Phillip Pearl and they've been other confirmations of similar findings. Interestingly enough, they usually resolve even if you continue the drug. It's not clear exactly what's involved. Some people have suggested it might be related to intermyelitic edema that was seen in some animal models but not others, pre-clinically. But we do not have histopathology from patients in order to confirm that notion.

DR. HUDAK: Dr. Kaskel?

DR. KASKEL: There is some evidence about acute kidney injury in the newborn and the need to follow that over time to see what happens with yearly creatinines and determinations. I wonder if that could be a recommendation?

DR. HUDAK: Thoughts at the end of the table?

DR. STOJANOVIC: The only thing

currently to label is that it's renally adjusted. So for the reports that we see, we don't usually have creatinine clearance, and all of the cases have previous renal issues. But as far as the recommendation you asked, I think Norm is going to address it.

DR. HERSHKOWITZ: Again, I'm a little disabled by being in a bad position of not hearing, so I'm thinking that you're asking if this renal signal is a real signal. I mean, at the moment we do not feel that this -- we can both continue monitoring it in the post-marketing data, but we didn't get much of a signal in the control trials. And again, these are the sickest of the sick.

I want to remind you, first of all, infantile spasms, and it's not only treating your run of the mill refractory seizures. We specifically recommend that you have to have failed several, although we don't define several, but we don't have any labeling that describes it, several other anticonvulsants. So these are the

sickest of the sick. We'll follow it in post-marketing, but we don't think that there's any indication for an action or including it in the REMS or anything.

DR. WHITE: Thank you.

DR. HUDAK: Okay. I think we are ready to vote on the recommendation by FDA to continue routine monitoring. Alright. We'll start with Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. MOON: Dr. Moon. I concur.

DR. DAVIS: Jon Davis, concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. HAVENS: Peter Havens, concur.

MS. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White, concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. MINK: Jon Mink. I concur.

DR. KASKEL: Rick Kaskel. I concur.

DR. BAKER: Susan Baker. I concur.

DR. TURER: Christy Turer. I concur.

DR. WALKER-HARDING: Leslie Walker. I concur.

DR. HUDAK: Okay. I think that's unanimous. So we will take a quick break until we regroup at 3:50.

(Recess)

DR. HUDAK: See if we can get started. Let's see if we've got the critical people at the table. I don't know who those are. (Laughs) They're coming. Okay. So, we're turning to the section of the meeting, which is our device section, hosted by our Center for Devices and Radiological Health.

And, our first presentation is going to be on the Impella Right Percutaneous System. This is an Initial Post-Market HDE Review, and Dr.

John Laschinger, Medical Officer of Structural Heart Devices Branch, Division of Cardiovascular Devices will be providing the overview.

At the table, we have other FDA folks who might want to introduce yourselves.

DR. WU: Changfu Wu, Office of Device Evaluation (CDRH).

DR. AGGREY: George Aggrey, Office of Surveillance and Biometrics, Division of Epidemiology.

MS. BAUER: Kelly Bauer, Office of Surveillance and Biometrics, Division of Post-Market Surveillance.

DR. HUDAK: Okay. I think we're ready.

DR. PEIRIS: Vasum.

DR. HUDAK: Yes? Oh, one more. I'm sorry.

DR. PEIRIS: Vasum Peiris. I'm the chief medical officer for pediatrics and special populations, with the Office of the Center Director, CDRH.

DR. NELSON: No, but I just want to

point

Out that there is now a chief pediatric medical officer at CDRH. So, I just wanted you to -- (Chuckles). Vasum's a pediatric cardiologist.

DR. HUDAK: Congratulations. Welcome.

DR. LASCHINGER: I'm John Laschinger. I'm also a medical officer at CDRH, Structural Heart Device Branch. And, as was just said, this is the first presentation of the Impella Right Percutaneous System. As a result, I'm going to just go into a little bit more detail this time around about some of the clinical data, not just the complications that we've seen.

The Impella RP System is a minimally-invasive miniaturized percutaneous circulatory system for the right ventricle. The main components are a 22 French micro-axial flow pump catheter and the Impella Automated Control Unit, and it's designed to provide greater than 4 liters of flow per minute.

As shown here, it's inserted through the femoral vein, usually on the right side. And, the

inlet area for the pump lies in the inferior vena cava, with the outlet in the main pulmonary artery. It has been designed through 3D CT human anatomic fitting studies, to be appropriate for body surface areas greater than 1.5 meters squared, which relates to approximately the age of 15 and above, which is why it's also for pediatric use.

The Impella RP System, as you note here, the indications for use are shown. As you note, it's a temporary device for up to 14 days of use for adult or pediatric patients above 1.5 meters squared, body surface area, who develop acute right heart failure or decompensation following LVAD, or left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery. The boxes on the right show the plausible pediatric populations that might need this device as a support mechanism for their right heart.

The humanitarian use designation was approved with an annual distribution number of

4,000 patients per year. There were 292 devices sold in the U.S. in 2015 and 143 implants, none in pediatric patients. The Recover Right Trial was the trial used to approve this device as a non-randomized safety and probable benefit study.

After the patients were assessed for eligibility, approximately -- well, exactly 30 patients were enrolled. Eighteen in Cohort A were right RV failure post LVAD insertion, and 12 in Cohort B, which were RV failure post acute myocardial infarction shock, postcardiotomy, or post-transplant. All 30 patients were treated with the Impella RP, were followed the 30 days post pump removal or hospital discharge, whichever was longer.

The major patient characteristics and major hemodynamic characteristics are shown in this slide. As you note, the youngest patient was 24 years of age, overwhelmingly male, and at 40 percent African American. The mean BSA was 1.94 meters squared, and most of these patients had adult-type cardiac disease and comorbidity, as you

can see.

The number of inotropes per patient were 3.2, cardiac index was 1.8, and the pulmonary capillary wedge and CVP were elevated as part of the hemodynamic characteristics prior to device insertion. There were no significant differences between Cohorts A and B that were unrelated to their cohort assignment.

As we look at some of the procedural characteristics, all the devices were inserted through the right or the left pulmonary -- I'm sorry -- femoral veins. The blood loss in over 90 percent was less than 50 milliliters for both the sheath insertion and for the pump insertion. The mean duration of support was just over 3 days, and the average device flow was about 3.3 liters for patients in both cohorts.

At the end of the trial period, a time of either days post pump removal or discharge, whichever was later, percent of patients in Cohort A -- that was the RV support following LVAD -- were alive. The vast majority of those were

discharged as well. And, on Cohort B, 56 percent were alive, with the majority, again, alive at discharge or with no deaths between weaning and discharge.

Safety endpoints, again, showed the deaths were different in Cohort A and B, as would be expected, being lower in Cohort A used during concomitant LVAD use, whereas, in Cohort B where there was either right ventricular damage from myocardial infarction or transplant rejection, there was a lower survival. Bleeding was similar in both group, and there were no significant differences overall between the two cohorts.

After device insertion, Cohort A and Cohort B, the average cardiac index rose from just under 1.8 liters per minute up to just over 3 liters per minute in both groups. There was a concomitant decrease in CVP from the range of about 20 down to 12, and the average LVAD flow in patients who did have LVADs rose also about a liter per minute for the LVAD. The number of inotropes that the patients required right after

pump implant also fell precipitously over the time of support and remained low afterwards.

The top left shows the plasma-free hemoglobin while the device was in place, and there was no evidence of severe hemolysis in these patients. RV function on the bottom left improved significantly in most patients who were supported. And, on the right, this just is a historical comparison to another HDE-approved device, the CentriMag RV Assist System, which shows that the mortality achieved in this study was substantially higher than that achieved during the CentriMag trial that led to approval of the CentriMag device for RV support.

The reason we approved this for a pediatric population is because we were able to extrapolate for pediatric sizes down to 1.5 meters squared body surface area and basically showed that in patients of that age range, that the average BSA for the children 15 to 21 are shown on the top, starting at 1.57 for a 15-year-old and going up to 2.0 for a 21-year-old on average.

When we look at the data, breaking it down into various body surface area ranges that would cover the pediatric population on the bottom left and bottom right, shows that, really, for the most part, the size that would be expected for a 15- to 21-year-old had similar results to all patients when taken as a whole, with no significant differences noted. On the bottom right, there is a deterioration in results as you get smaller, and that's pretty much seen with most LVAD-type procedures in the literature.

Humanitarian use designation was granted on July 13, 2012, and the IDE was approved on November 8, 2012. The HDE approval for the humanitarian device exemption was finally granted on January 23, 2015.

There are two post-approval studies going on to monitor the safety and probable benefit of this device. The first is the RP Prospective Study, and that's a prospective, single arm, multicenter study in patients with acute right heart failure or decompensation after

left ventricular assist device implantation, post myocardial infarction, post heart transplant or post open-heart surgery in patients with a body surface area over 1.5 meters squared.

This is going to enroll 30 patients at 15 sites in the U.S. and follow them for 30 and 180 days post explant. Thirteen patients have been enrolled currently, and the average age is 63 years with a range of 46 to 81 years. Knowing how prompt that we were not likely to enroll many or any pediatric patients in this, a study -- we also asked the sponsor to do a second study, specifically centering on pediatric patients.

And, basically, any pediatric patient that is implanted in the United States over the next 5 years will be reported as a retrospect of single arm, multicenter study. So, anybody less than 18 years with a body surface area over 1.5 that develop right heart failure after device implantation post myocardial infarction, heart transplant or heart surgery that is supported with the Impella RP will be reported, up to 15

pediatric patients in total or all pediatric patients supported with the Impella RP at a minimum of five sites over 5 years, whichever comes first. There's two pediatric sites that have been trained and received IRB approval for HUD use of the device as of January 2016. However, no patients have been enrolled yet.

Literature search was done between the dates shown, and the only thing we found was the actual report of the Recover Right Study which reported the results that you just saw and presented to you here today. We also did MDR search of criteria for the Impella RP, again, between the dates shown in the slide here. And, two MDRs were found with no pediatric patients involved in either. Both patients were 54-year-old males, separate patients, not the same.

One of them was a death in a patient who had a device inserted 16 days after an LVAD. He had continued low-grade bleeding from the site of insertion and required a total of 4 units of blood

over the next 14 days. His condition continued to deteriorate and the family decided to withdraw support after that time, and he died.

The second patient was 7 days into support when he had an anticoagulation disruption which led to a clot formation on the inflow site of the cannula. The device was removed, the patient was taken off the device and survived without complications.

The FDA recommendations and questions to the PAC are summarized on this slide. We recommend continued surveillance and will report the following to the PAC in 2017: The annual distribution number, the Post Approval Study (PAS) follow-up results, the literature review, and the MDR review. Does the committee agree with the FDA's conclusions and recommendations? (Pause) Thank you.

DR. HUDAK: Thank you, Dr. Laschinger. So, we've got several hands up.

DR. WHITE: Very quick, for clarification. Pediatrics for devices is up to --

DR. LASCHINGER: Up to the 22nd birthday.

DR. WHITE: 22nd birthday?

DR. LASCHINGER: Yes, sir.

DR. WHITE: And, the perspective study that you outlined in the report post approval study for pediatrics says pediatric patients 15 to 17. Is there a reason that you don't want to go up to 22?

DR. LASCHINGER: Yes. I think we probably will ask the sponsor to go up to 22. I think the reason is, is that most of those patients won't be done in a pediatric hospital. They'll be reported through the adult system. So, they might be included on the adult side if we see them.

But, if there is a patient implanted in the pediatric hospital that's over the age of 18, we certainly would expect that to be reported.

DR. WHITE: Thank you.

DR. HUDAK: Dr. Hoehn.

DR. HOEHN: My only question is that the

68 percent bleeding rate seems like a high complication rate compared to stuff like ECMO. So, I didn't know if there was any sort of historical controls that compared something like this device to ECMO.

DR. LASCHINGER: Yes. The bleeding that typically was seen was less than 25 cc, and it was from the puncture side of the vein, either the time of sheath insertion or the time of the device insertion. Ninety-five percent of the patients had less than 50 cc of total blood loss.

DR. HOEHN: So, it was groin bleeding.

DR. LASCHINGER: Yes.

DR. HOEHN: It wasn't bleeding that required them to take him off of the device or anything, right?

DR. LASCHINGER: No.

DR. HOEHN: Okay. Thank you.

DR. HUDAK: I thought I saw another hand.

DR. MOON: I got one.

DR. HUDAK: Okay, Dr. Moon.

DR. MOON: Is it mandatory that we review these things every year? I suspect by next year we'll have two people, two patients.

DR. NELSON: The legislation has the word annual in it, and this would be an example where if, you know, Vasum and -- I've talked about this -- that if we had the flexibility, we probably would have said let's wait another year and not present it. Whether we can review it and see if there's any way to do that absent of legislative change is an open question. I suspect not, because the word annual is pretty concrete. So, you're right, and, you know, the data is sparse. So, yes, it's not that useful, but it is what it is.

DR. HUDAK: So, Dr. Nelson, you renew my faith in government. Dr. Cnaan.

DR. CNAAN: Do you know if the sponsor has any other pediatric sites except the two identified?

DR. LASCHINGER: Just the two, so far.

DR. CNAAN: Do they intend to identify

trends of others?

DR. LASCHINGER: Yes, they intend to use the device if it's indicated. They haven't had the opportunity or, I guess -- not the opportunity but the misfortune of having to use it as of yet. But, they do have the ability to use it if they need to.

DR. MOON: I can address that. I think most pediatric sites are associated with an adult site, where at the adult center there will be somebody who can put this device in and he would go help the pediatric surgeon.

DR. HUDAK: Go ahead.

DR. PEIRIS: I'll address that last comment maybe first. I was going to talk about something else. But, the issue with respect to where the sites are, I think, is important, especially as we've begun to understand how can we most effectively and efficiently collect pediatric-related data. So, with most pediatric congenital and cardiovascular centers, the high-volume centers certainly are independent,

freestanding children's hospitals that are usually quaternary congenital and cardiac centers.

There are a few that certainly have both adult and pediatric services that are not specific to a pediatric quaternary center. And, that, I guess, the scenario that you mentioned certainly can apply there. But, higher volumes and higher likelihood of collecting data more efficiently will occur at those quaternary centers if we are able to engage them.

The other point that I wanted to bring up is the point that Skip has already alluded to about the utility of discussing these types of presentations, especially if we don't have the pediatric-related data. I think there is some utility with respect to the PAC members understanding our process by which we are collecting pediatric data and possibly discussing how we could be more efficient in that process. At CDRH, we definitely want to be very transparent about this. We are seeking to improve device labeling and indications for pediatrics, so I

think that part of it is also useful.

DR. HUDAK: Dr. Turer.

DR. TURER: I'd like to echo the statement about it would be nice to have historical controls to compare the data to, so not just another RV assist device but, you know, the standard of care and the current outcomes associated with it, I think, would be really helpful.

The other thing kind of along with -- we don't have the children's data. We have cardiologists using Impella at our children's hospital. I don't think it's the right-heart one though. So, one of the questions that I had is, are those zero pediatric patients zero pediatric patients enrolled in the trials versus how many total pediatric patients has this device been used in?

DR. LASCHINGER: No, the trial is designed to capture all pediatric use of the RP system. So, that's why it's a retrospective study. The company's going to report any- they

know whenever a device is used and put in, and, so, they're going to report all pediatric use at all pediatric hospitals for the Post Approval Study 2.

So, ages 15 to 18 or so, whatever children come to a pediatric hospital, are going to be reported to the FDA as a separate study. So, those all will be reported. There has been no use though yet in one of those pediatric hospitals, and nobody from the age of 18 to 22 has been implanted in one of the adult hospitals. So, that's why we have no pediatric use as of yet.

DR. HUDAK: Dr. Nelson?

DR. NELSON: It just occurs to me, based on your question, to just provide a little background about what gets a device to the Pediatric Advisory Committee review. So, there's really two components. One is that it's a humanitarian-use device, but not all pediatric humanitarian-use devices go to the Pediatric Advisory Committee. So, whether or not this other device is a pediatric HUD or not would be the

first question.

The second question is whether the sponsor has asked for an exemption from the prohibition against profit. And, the issue of device development has been a very difficult one over the years, contrary to the success in drugs where you have the incentives and the requirements that have stimulated a lot of drug development.

Device development in pediatrics has been hard to do, because the ability to protect intellectual property and so on and so forth is much more complex. And, so, the incentive is to allow a company to take a device if they develop it and market it in pediatrics, to allow them to get a profit. And, that's a smaller group necessarily than those that are only pediatric developed. So, in the world of all pediatric HUDs, they're all not coming here. It's just those that have that profit exemption.

DR. LASCHINGER: To answer your question about the comparing (Dropped audio) -- we looked at. We do look at the historical comparators that

are available in this population. And, unfortunately, for children, the only real devices available up to now were the CentriMag device, which this device outperformed ECMO, which also, if you look at the historical data for ECMO, the survival rates in conjunction with both RV and LV failure are fairly low as well and also had more bleeding complications associated with the strokes and those kinds of things that you won't see with a pure RVAD device, because of the protection of the pulmonary circulation.

And, then, we also look at, you know, just what would be the expected outcome of these patients without RV assistance, and it's dismal. So, we take all of that into consideration in our review of these things and we had the equipoise to have a two-arm trial in approving this device. So, that's why we do it.

DR. PEIRIS: Thank you. Vasum Peiris. And, just also to add to what John has already mentioned, there are other Impella devices. Just to clarify that. This is specific.

DR. LASCHINGER: Yes. They are left-side devices that go in through the femoral artery and go in across the aortic valve and support the left side of the heart. The smallest is a 2.5-liter flow device, and that would probably enjoy some off-label use, I would assume, in pediatric populations for assistance.

It was just approved last week, the whole range of devices, from 2.5 to 5 liters of flow per minute, a family of devices, specifically for left ventricular assist. So, those devices are now approved for use in left ventricular assist and the same situation as we described here.

DR. HUDAK: Other thoughts? All right. Hearing none, I guess we can vote on the recommendation of the FDA to continue surveillance on these issues with the probable, possible report back in 2017, depending.

DR. NELSON: Are you suggesting in an election year we'll get a congressional change?

(Laughter)

DR. HUDAK: My faith in government isn't that much. All right. So, we can vote. All right. So, we'll start Dr. Walker-Harding.

DR. WALKER-HARDING: Leslie Walker-Harding. Concur.

DR. TURER: Christy Turer. Concur.

DR. BAKER: Susan Baker. Concur.

DR. KASKEL: Rick Kaskel. Concur.

DR. MINK: Jonathan Mink. Concur.

DR. CUNNINGHAM: Melody Cunningham. Concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. WHITE: Michael White. Concur.

DR. CELENTO: Amy Celento. Concur.

DR. HAVENS: Peter Havens. Concur.

DR. RAKOWSKY: Alex Rakowsky. Concur.

DR. TOWBIN: Kenneth Towbin. Concur.

DR. DAVIS: John Davis. Concur.

DR. MOON: Marc Moon. Concur.

DR. DRACKER: Bob Dracker. Concur.

DR. CNAAN: Avital Cnaan. Concur.

DR. HUDAK: Okay. Thank you. So, our next topic will be the annual update on the Medtronic Activa Dystonia System therapy. And, I guess we have a little bit of technical things to do before this comes up. Gives a chance for new people to come to the table and get set.

MS. BRILL: At this time, I'd like to remind that we have two recusals. As stated this morning, we have Dr. Moon and Dr. Mink. And, I note for the record that Dr. Moon has stepped away from the table. Yes, he has departed. And, Dr. Mink --

DR. NELSON: We generally just let them pull their chair back and note that they're absent from the table, but if he wanted to sort of take a walk, that's really up to you.

MS. BRILL: Thank you, Skip.

DR. HUDAK: Okay. So, perhaps the folks who joined the table at the end here can introduce yourselves while they are - they've got it up. Okay.

MR. MARJENIN: Hi. I'm Tim Marjenin. I'm the chief of the Neurostimulation Devices Branch in the Division of Neurological and Physical Medicine Devices and the Office of Device Evaluation.

MR. ANDERSON-SMITS: Hi. I am Colin Anderson-Smits. I am the branch chief of Epidemiology in the Office of Surveillance and Biometrics.

MR. MILLER: Andrew Miller, Office of Surveillance and Biometrics, Division of Postmarket Surveillance.

DR. HUDAK: So, presenting we have Dr. Millin from the Product Evaluation Branch III of the Division of Postmarket Surveillance, Office of Surveillance and Biometrics.

DR. MILLIN: Well, I can --

DR. HUDAK: Of course, the devices would fail for the device presentation, but.

DR. MILLIN: I can introduce myself while --

DR. HUDAK: The panel can see. The

audience cannot.

DR. MILLIN: It could be. So, I'm Courtney Millin and I'm an MDR analyst in the Office of Surveillance and Biometrics, within the Center of Devices and Radiological Health. I'll be presenting the annual safety update on the use of the Medtronic Activa neurostimulator for treatment of dystonia in pediatric patients. This is the third time that this device has been reviewed by the panel. In a minute we'll have some slides.

Can you see? Not yet. Okay. Maybe I can give you guys the device description, or shall we rather wait? Go ahead? Okay. There will be an image in a minute. But, the Activa system consists of three main components, including a neurostimulator, extension, and lead. The implanted neurostimulator is the power source for the system. This small pacemaker-like device contains a battery and is programmed to send electrical signals to manage dystonia symptoms.

The extension is an insulated wire,

placed between the scalp and the skull, that connects to the lead and runs behind the ear, down the neck, and into the chest, below the collarbone where it connects to the neurostimulator. The lead is a set of thin wires covered with a protective coating that carries the stimulation signal to the electrodes that deliver the signal to the brain. Part of the lead is implanted inside the brain. The rest of the lead is implanted under the skin of the scalp. And, there is sort of the top half of the image.

The Activa neurostimulator was originally approved for the treatment of parkinsonian tremor in 1997 and subsequently received HD approval in 2003 for the treatment of dystonia in adults and pediatric patients 7 years of age or older. The specific dystonia indications for use are provided in this slide.

The HDE was approved with an annual distribution number of 4,000 devices. Twenty-four devices associated with the dystonia indication were sold in 2015. A total of 887 devices were

implanted, 159 of which were implanted in pediatric patients. There were 3,365 active implants in 2015, including 601 active pediatric implants.

Many and most of you have been on the Pediatric Advisory Committee for various different pediatric HDE presentations and are likely familiar with CDRH adverse event reports, or MDRs. This slide provides a brief reminder of the limitations of MDR data.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including underreporting, data quality issues, like the potential submission of incomplete, inaccurate, untimely, unverified, or biased data.

In addition, incidents or prevalence of an event cannot be determined from this reporting system alone due to potential underreporting of events and lack of information about frequency of device use. Finally, it's not possible to definitively determine a causal relationship

between an event and the device based on MDR data alone.

The MDR database houses MDRs submitted to the FDA by mandatory reporters, including manufacturers, importers, and device user facilities as well as voluntary reporters such as healthcare professionals, patients, and consumers. For the purpose of this analysis, the MDR database was searched by date of report entered, brand name, product codes, and presubmission number. Using this search criteria, we identified 333 MDRs pertinent to the dystonia indication.

This table presents the event types of the 333 MDRs associated with the dystonia indication, broken down by patient age. There were a total of 56 pediatric MDRs associated with patients ranging in age from 2 to 21 years old. The average pediatric age was 15.7 years old, which is similar to the average pediatric age in the 2015 PAC data which was 15.6 years old.

There were 223 MDRs associated with adult patients and 54 MDRs in which the patient

age was not reported and could not be determined. The three death reports were associated with two unique events and did not provide enough information for us to determine patient age. More information on these death reports will be provided in a slide in a few minutes. The number of deaths this year is similar to what was reported in the previous PAC years.

For comparative purposes, the total number of MDRs for the 2014, '15, and '16 PAC data sets are presented in this table. The dates included in each PAC reporting period are presented below the table. Please note that the 2014 PAC included more than 1 year of data. Also, please note that the PAC reporting periods do not coincide the calendar years.

The total number of MDRs increased through the 2014, '15, and '16 PAC data sets. The larger cumulative number of patient currently implanted with the device may be a contributing factor to this apparent increase in MDRs over time. In all three PAC data sets, the majority of

the MDRs were associated with adult patients. The percentage of pediatric reports within the 2015 and '16 PAC data sets was also very similar.

Please also note the relatively large number of reports associated with patients of unknown age. Patient age could not be determined for these reports, and it's possible that some could be associated with pediatric patients. Consistent with the 2014 and 2015 PAC data sets, there were more reported patient injuries than malfunctions. The majority of the MDRs originated from inside of the U.S. This is consistent with the reporting patterns seen in the 2014 and '15 PAC data sets, and patient gender was available in 307 MDRs.

There were three MDRs reporting patient death associated with two unique events. The patient ages associated with the death reports are unknown. In the first report, the patient died secondary to comorbid conditions, including Batten's disease, dystonia, and seizure disorder as well as postoperative complications, including

fever, respiratory distress, hypoxia, and infection. It's possible that this is a pediatric death, since Batten's disease is a rare and fatal autosomal recessive neurodegenerative disorder that predominantly begins in childhood.

In the second report, the patient experienced postsurgical hemorrhage at the site of the lead tip. The patient went into a coma and required life support as a result of the unrecoverable brain damage. The patient was subsequently taken off of life support and died.

A more in-depth review was conducted on the MDRs associated with pediatric patients. The pediatric reports were individually reviewed to identify events that were clinically significant or concerning as defined by CDRH clinicians and reviewers. This table shows these clinically-concerning adverse events and how frequently they were reported. I'll discuss each of these event categories in detail in a moment.

It's important to note that a single MDR may be associated with more than one patient

problem. Therefore, more than one contributing factor may have been associated with each of the events presented in the table. Additionally, a unique event may be associated with multiple MDRs, since patients are often bilaterally implanted or reports can be received from multiple sources, such as a voluntary reporter as well as the manufacturer.

The pediatric MDRs reported 24 device replacements. In the 24 reports that included both device explant and replacement, the most frequently reported patient problems were in impedance issues and lead fracture. Time to replacement could be calculated in 10 of the 24 MDRs and ranged from the day of implant to 2.73 years after implant, with an average time to replacement of about 11 months.

There were eight MDRs that reported device explant without device replacement. Six of these reports were associated with infection and two were associated with mild stroke. More information on the stroke and infection MDRs will

be provided in a later slide.

Worsening or return of dystonia symptoms was associated with several different device problems. The reported problems that contributed to worsening or return of symptoms are provided on the slide. The most frequently reported contributors were battery and charging issues and impedance issues of unknown causes. The majority of these issues were resolved, though device replacement was required in 10 cases.

There were 10 pediatric MDRs reporting infection. Limited information was provided on the potential causes of the infections. In some of the infection reports, organisms associated with the infection were provided, and these are presented on the slide.

The infections were treated with antibiotics, oral and intravenous, debridement, and device explant. One MDR reported that a patient may have experienced cognitive changes due to infection. The MDR did not indicate if the cognitive changes were transient or not, and no

information on the patient outcome was provided. All of the infections resulted in full or partial device explant.

There were nine pediatric MDRs related to battery and/or charging issues. These reports where associated with a variety of contributing factors which are presented on the slide. These battery-charging related issues most frequently resulted in a return of patient symptoms as well as pocket revision, loss of therapy, and device replacement.

Potential growth-related issues were reported in six MDRs, associated with mechanical issues, multiple system revisions due to patient growth, and possible tension on the extension due to growth. The ages of the patients associated with these reports range between 16 and 17 years old. Time to event from date implanted was not able to be calculated, based on the information provided in the MDRs.

There were six pediatric MDRs associated with potential EMI, from both unknown sources and

exposure to a standing X-ray. Based on the limited information provided in the MDRs, the impact of EMI on the device is unclear but may be associated with inadvertently changing device settings or turning off the device.

There were five MDRs associated with lead break or fracture. All of these MDRs resulted in device replacement. The types of lead break fracture are presented on the slide and include intraoperative lead fracture, electrode fracture of unknown cause, and lead break possibly due to patient growth.

Stroke was reported in three MDRs. In one event, a 15-year-old patient experienced a mild stroke after implant. No additional information on patient outcome was reported. In the second event, a 10-year-old patient experienced a left-brain stroke at the time of implant which resulted in the limited ability to move her right arm and leg as well as inability to speak.

After significant rehabilitation, the

patient was able to speak in a faint voice and was able to walk, although not for long distances. The patient was receiving therapeutic effect from the device and was doing better than her baseline prior to the device implant, despite the stroke. Despite follow-up, no information regarding the potential factors that contributed to the strokes was provided in the MDRs.

There were three MDRs associated with -- I'm sorry -- reporting cognitive issues. In one event, it was reported that a patient had altered mental status, potentially due to a device-related infection. In the second event, it was reported that the patient was experiencing mood changes due to internal globus pallidus stimulation.

The patient's schoolteachers noticed a significant change in the patient's behavior. The patient turned off the device, which resolved the mood changes but resulted in diplopia. The device was explanted and replaced which resolved the mood changes and diplopia.

In summary, a total of 56 MDRs reporting

39 unique events were associated with use of the Activa neurostimulator in pediatric patients. A return or worsening of dystonia symptoms was the most frequently reported pediatric patient problem. This type of patient problem is often indicative of an issue that can be resolved. The labeling does address the issue of symptom return worsening, and the events are known to occur with the use of other neurostimulators.

Other reported patient problems, including infection, are noted in either the device labeling or clinical summary. The most frequently reported device problem was impedance issues. The device labeling states that issues with open circuits or high impedance can occur without warning, and impedance issues are also known to occur in other neurostimulators.

Other device problems that occurred within the MDRs are either noted in the device labeling or are known issues with neurostimulator devices in general. In summary, no new device or patient problems were identified in the 2016 PAC

data.

I'll now present the information on the literature review completed by the Division of Epidemiology. The literature review was performed to evaluate adverse events following the use of Activa for primary dystonia in pediatric patients.

A string of search terms identical to what was used in the previous literature reviews, and listed on the slide, was used to search the PubMed and EMBASE databases for the 12-month period. Articles were only included if they reported on outcomes specific to primary dystonia and within pediatric populations.

The search yielded 46 articles, 45 of which were excluded for the various reasons listed on the slide. There was only one article that met our inclusion criteria. The pertinent article was authored by Rizzi et al and included 11 patients with an age range between 8 and 21 years and a follow-up duration in the range of 1 to 15 years.

In these observational data, mortality from causes other than deep-brain stimulation was

9.1 percent. No adverse events related to DBS were reported. The complication rate was 23 percent, 18 percent of which was ascribable to internal pulse generator (IPG) replacement. The authors did not report individual complications.

In summary, no novel safety events were detected in the literature published since the last PAC. These findings are consistent with the conclusions from the literature review conducted for the previous PAC meetings.

So, FDA recommends continued surveillance and will report back to the PAC in 2017. And, we'd like to note the committee agrees with FDA's conclusions and recommendations.

DR. HUDAK: Thank you. We're open for discussion. Yes.

DR. RAKOWSKY: Thank you, Dr. Millin. Can you go back to Slide 4. Just walk through the numbers there. The number sold was 24, but number implanted was 887. Why the discrepancy there?

MR. MARJENIN: This is Tim Marjenin. More than likely it's due to off-label use of the

device. So, the DBS devices that Medtronic has are labeled for dystonia. They're also labeled for Parkinson's. They're also labeled for obsessive-compulsive disorder. So, there are multiple indications for which patients might be implanted.

DR. RAKOWSKY: So, they're only reporting for those 24, or all the safety is for any use of this device?

MR. MARJENIN: So, the annual distribution number that's cited here -- so, the actual dystonia-labeled devices would be 24, but the total number of devices implanted would be the 887. And, that would cover all of the indications, more than likely.

DR. HUDAK: Yes?

DR. HAVENS: Peter Havens. On Slide 8, thinking about the malfunctions, is there a way to get a sense of the rate of malfunction. The number seems to be increasing. But, if that's just a function of the number of devices implanted, it doesn't matter?

DR. MILLIN: It's really hard to interpret rate information with MDRs, because we don't have good denominator data. And, there are so many biases with reporting. So, we try to think of it more as a qualitative snapshot versus quantitative.

From reading these reports, we didn't see anything that was concerning or that indicated an increased level of concern or -- you know, we can't use the word rate, but, I don't think that we saw anything that was like significant with regard to rate. But, with MDR data, we can't really definitively respond to that.

DR. HUDAK: Dr. Campbell.

DR. CAMPBELL: Hi. Jeff Campbell. What do you all regard as a device? So, when you talk about explanting, we're replacing it --

DR. MILLIN: I'm sorry. I couldn't hear you at the beginning of your question.

DR. CAMPBELL: I'm sorry. So, there's a generator and there's a lead, and the implication to replacing one versus the other is very

different. What is a device? So, when you say that a device was explanted versus replaced.

DR. MILLIN: For the purposes of this analysis, any time any component of the device was explanted, we considered it an explant. That was because in some of the MDRs it was unclear which component was explanted, and if it was bilaterally explanted or -- you know, there was just limited information. So, we decided to just err on the side of caution and include all of them as explants. Although, I see your point. I wish we could do better dividing that apart.

DR. CAMPBELL: Sort of a second question.

DR. MILLIN: Sure.

DR. CAMPBELL: Many of the neurosurgical devices that we implant have a high mechanical malfunction rate the younger they're placed. Are you able to look at lead malfunction, by age, to understand whether or not that's true with this device as well, so that more leads would tend -- what we would think would break the younger you

are when they are implanted?

DR. MILLIN: Sort of like potential growth related issues, or like the duration of use?

DR. CAMPBELL: Growth.

DR. MILLIN: Growth. Well, we did see some MDRs that we thought were potentially associated with growth. Those were in some of the older patients. They were the 16- and 17-year-olds. But, again, MDR data is not perfect. We did look at it by age, and there was no trend towards younger patients in what we saw.

DR. CAMPBELL: So, they're breaking in the 17- year-olds because they were placed when the patient was 7 and they grew for 7 years, probably. And, so that's --

DR. MILLIN: I imagine so.

DR. CAMPBELL: -- what we see with our other devices.

DR. MILLIN: Yes, we tried to calculate the time to event, you know, from implant, like the duration, how long that the patient was

implanted. And, we weren't able to based on the information in the MDRs. But, I think you're right.

DR. HUDAK: So, this does look very familiar to the prior year's presentation, as you pointed out. So, thank you. Hearing no further discussion, we're ready to advance to Slide 26 and vote on the recommendation for the FDA to continue monitoring of this device and report back in 2017 on the following four features. So, go ahead and vote.

MS. BRILL: So, we're needing like two more?

DR. HUDAK: Two people have left. Okay. So, we'll go around. So, we'll start out with Dr. Cnaan.

DR. CNAAN: I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. DAVIS: Jon Davis. Concur.

DR. TOWBIN: Kenneth Towbin. Concur.

DR. RAKOWSKY: Alex Rakowsky. Concur.

DR. HAVENS: Peter Havens. Concur.

DR. CELENTO: Amy Celento. I concur.

DR. WHITE: Michael White. Agree.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. KASKEL: Rick Kaskel. Concur.

DR. DANIELS: Susan Baker. Concur.

DR. TURER: Christy Turer. Concur.

DR. WALKER-HARDING: Leslie Walker. Concur. Leslie Walker-Harding. Concur.

DR. HUDAK: Let's be clear. Okay. So, we are finished with the second, and we're on to the last item for the day. Okay. So, if I could have the --

DR. NEULAND: I'm Carolyn Neuland. I am the chief of the Renal Devices Branch in the Office of Device Evaluation.

MS. BUSHEE: Hello. I'm Cynthia Bushee in Office of Surveillance and Biometrics in the Division of Postmarket Surveillance.

DR. HUDAK: Okay. Dr. Silverstein, introduce yourself and get started.

DR. SILVERSTEIN: Good afternoon. It's always advantageous to present at the very end of the day. And nephrology is always a topic --

DR. HUDAK: You have a very enthusiastic audience at this point.

DR. SILVERSTEIN: Yes. I'm just happy to have an audience. Nephrology is always a topic you want to hear at this time of the day. So, my name is Doug Silverstein. I'm in the Renal Devices Branch. I'm a medical officer in the Office of Device Evaluation.

This is the second year we'll be talking about the Liposorber device for children with a renal disease. The indications for use for the pediatric HDE we'll be discussing are the Liposorber LA-15 System is indicated for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS), when standard treatment options, including corticosteroid and/or

calcineurin inhibitor treatments are unsuccessful or not well tolerated and the patient has a GFR of at least 60 mL per minute or the patient has nephrotic syndrome and primary FSGS after renal transplantation. So, GFR is glomerular filtration rate, and it's a measure of renal function.

A little bit of background. We presented this last year. Just to redux this, FSGS is a kidney disease resulting in severe proteinuria and usually nephrotic syndrome. The majority of patients who develop FSGS reach end-stage renal disease, which means they need either dialysis or need a kidney transplant within 10 years of the initial diagnosis. But, I'll just make a very brief point. The disease is a very heterogeneous disease, does not describe one group of patients, includes patients who may have genetic predisposition or patients who have a different type of histology from other types of patients.

Previous reports show the probable benefit in safety for adults and children with

FSGS treated with the device who were resistant to or intolerant of standard medical therapy. The HDE for FSGS was approved in 2014, and the sponsor is conducting a post-approval study to assess the probable benefit and safety of the device in children in the intended use. The PAC was presented with a summary of the HDE in March of 2015, and this is an annual update.

Just a brief description of the device, the way it works. I'm just trying to get my pointer here to work. It doesn't seem successful, but, just basically, if you start out -- there we go. This is an extracorporeal circuit. So, the patient has a catheter and it's hooked up to an extracorporeal circuit, which is like a dialysis circuit.

So, blood is removed from the patient, it goes through a blood pump, and eventually goes through a filter which will then separate the plasma from the blood cells. The blood cells are actually returned to the patient. The plasma itself is what you want to actually act on. The

plasma, then, goes through the actual Liposorber columns. And, these are two columns that can trap LDL cholesterol and probably trap other products. So, eventually, the plasma is cleaned up, it is returned back to the patient and rejoined with the blood. This goes on for several hours. So, it's a classic extracorporeal circuit.

The postmarket study that the sponsor agreed to engage in includes assessment of safety, adverse events 1 month after the Liposorber treatment and while they're getting the treatment, and also assess the probable benefit, including the remission of nephrotic syndrome, which is a major predictor of disease activity and a predictor of outcome and renal function or GFR.

The patients had to be under 21 years of age, have a body weight of at least 21 kilograms. Just parenthetically, that was recently changed within the last few months to 18 kilograms to allow them to enter more patients into the study. But, I won't be discussing that particular change today.

The patients, as shown in the indications for use had FSGS and persistent nephrotic syndrome and were resistant to or intolerant to medical therapy and had reasonably good renal function. They received 12 treatments over a 9-week period of time, and we collected information in 32 patients. That was the plan. Four, so far, have been treated, and we collected adverse events, device malfunction, and a variety of other outcomes, which I'll be talking about.

So far, the sponsors have basically entered four patients into the study so far. You can see that the patient at the bottom shown in the red-bolded font has just started the therapy, basically, in August, and we don't have any other results than what was shown so far. So, basically, we just had baseline results.

So, walking through this a little bit, we have three patients who have been treated with the device. You can see the three patients on these three lines. And, we're looking at urine protein to creatinine ratio, which is a major

predictor of disease activity -- the lower the ratio, the better the patient is doing -- and estimated glomerular filtration rate, which is a measure of renal function.

We showed results here at baseline, before treatment started and then 0, 1, and 3 months after treatment started. So, as you can see, for Patient 1, the initial protein-creatinine ratio was 44.3. Anything over 1 is consistent with nephrotic syndrome, so this is a significantly elevated protein-to-creatinine ratio.

And, you can see over the period of 3 months the protein-creatinine ratio drastically reduced but still remained very elevated. The same thing happened in Patient 2. The results went down but still remained elevated. And, Patient 3 had the best results so far. It went down to 0.9. But, again, this is still elevated.

And, you can see by GFR, if you look at all three patients combined, generally what it shows is there was a stabilization of GFR. Some

patients went down, some patients went up, but the bottom line is if you put all three together there's really no reason to do a statistical analysis at this point. The GFR remained relatively stable.

So, the summary is, is that it seemed as if the proteinuria was resolving, to some extent, reasonably so -- again, these are patients who had no other option for therapy, and it looks as if GFR is at least preserved throughout the 3-month period of time. There weren't many reports of adverse events.

All these events that I'm showing on this slide occurred in one single patient over a relatively short period of time, over 2 months, and included leg cramps, bacteremia, diarrhea, left mandibular pain, possible infection, and left hip cellulitis. So, this table is adapted from that provided by the sponsor to protect some patient identifiers.

These events were all determined to be not reportable by the manufacturer, and we agreed,

even though they provided this -- in reports they provided to us along the way, we believe that these events were not related to the device, even though a couple of them may have been reported to be possibly related to the device.

But, we believe they were actually more related to two factors -- number one, these patients had nephrotic syndrome and there are certainly a number of adverse events that can occur in nephrotic syndrome, and second, the patients had a catheter in place in order to get the therapy. And, we all know that catheters are associated with a variety of types of adverse events. Regardless, all these adverse events resolved. Several of them require hospitalization, but, again, we did not believe these were related to the device itself.

Literature review didn't turn up too much information. There were two case reports in 2015 that together described two adults with confirmed or suspected FSGS. Not all patients are biopsied if they have a disease that is suspected

to be FSGS. And, they were treated with the Liposorber LA-15 System. They showed some clinical improvement, but the safety data was missing or minimal, which is very common for a case report.

There was one relatively large study by Muso et al in 2015. It was a prospective study of 58 adult patients with refractory nephrotic syndrome, so wasn't responding to therapy. Again, these patients all appear to have FSGS, although they weren't all biopsied. Among the 44 that were followed for 2 years, 25 percent achieved a complete remission, 47 in incomplete remission, and 27 percent no remission.

So, among all the patients, about 72 percent achieved some type of remission. Again, these are patient who were in relapse who were not achieving remission with their current therapy. Again, unfortunately, minimal safety data was available in this report.

As far as MDRs are concerned, a search of the MDR database resulted in two MDRs for the

analysis time period of November 2014 through the end of 2015. There were no MDRs for this device for this indication for pediatric patients.

There were two MDRs, including a death and a serious injury event, which I'll describe on the next slide, which were submitted under the MMY product code that includes devices such as the Liposorber device, but other types of extracorporeal devices. They were both reported in adults who were not undergoing apheresis for FSGS. So, again, just for that product code, the type of therapy but not this particular therapy.

In one report here on the left-hand part of the slide, there was a death report for a 59-year-old female who had multiple comorbidities, treated with the device under the MMY product code but not the Liposorber device. The death occurred after the sixth apheresis procedure, and there was really no clearly-stated device causality.

In the other one, there was an 83-year-old male who had a serious injury report who also had multiple comorbidities, experiencing

two adverse events during two treatments, one resulting in hospitalization, and the manufacturer stated in the MDR report that the events were related to concomitant medications.

And, as described in the talk before, MDRs are unfortunately riddled with concerns about whether or not everything is being reported. And, we don't always get all the information that we want, so we just receive the information that we get, and we can only analyze that.

The annual distribution -- just quickly -- there were three machines shipped to particular centers, and, similar to what was presented with the cardiac device, all of this has to occur in a children's hospital. This cannot occur in an outpatient dialysis center.

And, you can see that the Liposorber LDL absorption column were shipped, 114 pieces of those, the plasma separators, same number, and the tubing sets. So, some of these tubing sets and plasma separators and columns may not have been used in every patient, but they were just shipped

to the particular centers.

So, the FDA concludes that as of January 2016 four pediatric patients have received therapy for FSGS with the Liposorber device. Of the three patients that have finished a complete course of therapy, all exhibited a reduction in urine protein to creatinine ratio. Again, a marker of disease function showing an improvement while showing stabilization or improvement in their renal function as measured by GFR.

And, while some adverse events were not insignificant, as shown for that one particular patient, none were thought to be device-related but were rather consistent with that observed in the underlying disease or associated with the device such as a catheter that is necessary to receive the therapy.

So, we conclude that the benefit-risk profile to date supports the continuation of the postapproval study, and we recommend continued surveillance. The FDA will report the following to the PAC in 2017, the distribution number, the

follow-up results, including probable benefit and adverse events, literature review, and MDR review. And, so, our question to the panel is, does the committee agree with the FDA's conclusions and recommendations.

DR. HUDAK: Open for questions.

DR. DRACKER: In most lipopheresis or plasmapheresis trials, there's usually a sham arm where there's a nontherapeutic column used for the studies. Was that considered in this trial?

DR. SILVERSTEIN: It's a good question, and I figured somebody might ask that question. Within the pediatric nephrology world -- and I have a couple of colleagues here who are pediatric nephrologists -- it's extremely difficult to do randomized controlled trials or controlled trials. The reason that it's most difficult in this particular disease is not only is there a low incidence of the disease and prevalence, but also, as I mentioned before, FSGS is not a uniform disease.

So, FSGS includes five histological

subtypes but also includes various types of etiologies. There could be genetic factors. Dr. Kaskel like I said, a well-known expert on this, has written publications on this. And, even within those genetic predispositions, there are variabilities in outcomes. So, your question is a valid one, and I think we all would prefer to have a controlled study. But, I think it would be extremely difficult -- we discussed this with the sponsor -- to identify patients that would completely match those being treated.

There are some differences in outcomes related to the age at onset, which might have a lot to do with the factors I just talked about -- genetic predisposition and certain types of histological subtypes. So, although it would be preferred -- it would be the way to go here -- it would be very, very difficult to create a true match.

So, what we did was we allowed them to use the patients as their own controls and see how they did over time. If anything, this would bias

against the study, because the patient's already had disease for quite a long period of time, they probably had -- we don't know this for sure -- but, they probably had histological evidence of some degree of progression. And, therefore, we believe that, if anything, this might make it more difficult for the patients to improve or stabilize, because their trajectory was already on a downward path already. So, agree, it would be ideal, but, unfortunately, it wasn't something that would be feasible.

DR. DRACKER: Just to follow. I only ask because it's always been suggested that extracorporeal circulation and separation can induce some immune modulation by itself.

DR. SILVERSTEIN: That's an excellent point. And, actually, in the discussions we had with the sponsor about this, we talked about what the mechanism was that this would be actually improving the patients. And, we discussed this a little bit last year. So, the Liposorber LA-15 System is approved for children and adults who

have familial hypercholesterolemia. So, it removes the LDL cholesterol in patients who have significantly elevated LDL cholesterol, beyond that which would be responsive to statins.

So, the question we had, and we still have, is what exactly is this removing that would allow the patients to improve. What's the mechanism, what's the pathogenesis for the mechanism that would support the indication? And, we really don't have a great answer for that.

One of the issues that was brought up in response to what you just stated was are there immune modulators being removed. I think that's very, very likely, because immune modulators may not be the cause of FSGS, but they certainly ensue after the disease develops in which we know that inflammation is a major factor that results in progression of various types of kidney disease.

The only other factor that we thought about was that there has been a lot of literature in the last 4 or 5 years, showing that if it's a circulating factor -- one is called suPAR, little

S, little U, then capital P-A-R, which has been identified in some patients with FSGS, which seems to be maybe in inciting factor for FSGS, not all patients, and there are definitely other circulating factors.

So, it's possible that in some patients the device is removing this particular circulating factor or other ones. And, as part of their study they are going to be measuring suPAR levels. We don't have that data yet. And, it might be retrospectively interesting to see if the response was related in some way to the removal of the factor.

Again, small number of patients so far, but even if you had -- excuse me -- even if you had 100 patients, it's likely that the minority of them would have the circulating factor that you could measure. So, it's an excellent question, and we wonder ourselves what the mechanism is. But, there obviously is a removal of some kind of circulating factor and/or immune modulator.

DR. HUDAK: Questions. Dr. Turer.

DR. TURER: I probably won't have time to vote, because I need to go catch a plane. But, I do wonder. There is an entity called obesity-related glomerulopathy. It looks pathologically like FSGS, but it's distinct and improves with weight loss. So, I would highly recommend looking at BMI and changes, using the Metric, published in New England Journal at the end of 2015, with percent over the 95th percentile BMI.

DR. SILVERSTEIN: That's a great point. I really like that, and I think that we can easily ask them to include that. So, Carolyn, if you could just please take notes, because I can't take notes right now. But, obesity-related FSGS has certainly been described. There is histological differences between those patients and the patients who have other type of FSGS.

But, we can certainly -- they're collecting the weight and the height and -- it's interesting, that point never came up in our discussion, and I think we can definitely ask them

to do that analysis. It's a small subgroup. And, we can probably find out if the patients had obesity before they were entered into the study. Those patients usually do very well if they lose weight. So, it would be interesting to find out if they have any of those patients in the study. But, we can definitely ask them. I think that's relatively easy to do. Thank you. Enjoy your flight.

DR. HUDAK: Ladies first. Dr. Cunningham.

DR. CUNNINGHAM: Hi. I'm Melody Cunningham. Just related to the patients with familial hypercholesterolemia (FH) -- I mean, there are a fair number of pediatric patients. So, we certainly couldn't extrapolate benefit, but, I mean, same system you may be able to extrapolate some safety data and immunomodulation data.

DR. SILVERSTEIN: So, it's interesting you say that, because when we received the submission -- I know you guys all want to go home,

but I'll just briefly mention -- when we received the submission, we were trying to figure out how we can assess the safety for the patients with FSGS. There was not literature that would allow us to say is this a device that is safe for patients with FSGS.

So, what we did was something that we're trying to do a lot more in pediatrics, and Dr. Peiris knows all about this. He's involved in a project right now. We extrapolated data from the patients with FH. So, what we did was, we were able to extrapolate safety data from children with FH who were treated with the Liposorber device.

It was tricky, because we were trying to figure out -- and we spent a lot of time talking about this -- Carolyn, my branch chief, and I spent a lot of time talking about whether this was appropriate or not. But, we felt that patients with FH -- and the cardiologists here know this better than I do -- have significant comorbidities and risk factors that are somewhat similar to some patients with renal disease who do develop

cardiovascular disease. But, we felt, if anything, their cardiovascular disease was probably more severe, on average, than patients with FSGS who would be included for this particular indication.

Looking at that data, we actually were very encouraged by the safety profile of children with FH treated with the device. The types of adverse events were relatively infrequent and relatively mild, considering the patient population. Certainly, the benefit for those patients with FH was clear, because we were moving LDL cholesterol.

So, we were able to extrapolate that data and to use that to support the approval. Hopefully, as we get more information on this particular patient population, that will validate the safety information. So far, it looks very good. These patients are doing extremely well. But, we did include certain safety features into the study that would address maybe some unforeseen events that may occur in the FSGS population

versus the FH population.

DR. HUDAK: I think Dr. Kaskel had his hand up.

DR. KASKEL: Just a quick question, Doug, because we could talk for days on this. But, there's some new data by Alesoni [sic], that in the podocyte in patients with FSGS you've got some abnormal lipid involvement in the podocyte. So, this is interesting. And, two, we also know recently that in African Americans, that the two risk alleles for APOL1 who have FSGS, they go much quicker. It appears that that group may have these lipid abnormalities, more than those with one risk allele or non-African American. So, the potential down the line from this small group is very high.

DR. SILVERSTEIN: Yes. And, it's a good point. And, you and I both know one of our colleagues from where we have both worked in the past at Einstein, Dutch Schlondorff, did some research, actually back in the '80s, showing the effect of lipids on the mesangial cells, which are

important cells within the glomerulus, with the filtering unit.

And, this has sort of come back full circle with the APOL1 gene in relationship to FSGS and also for the hypertension. And, those patients do extremely poorly. So, the limitation of this particular study is that we're not doing the genetic profiles.

And, we discussed this at length with the sponsor. We wanted them to actually do genetic testing. It was just that there was a limitation of how much they could do. There were some financial resources and other issues. I mean, originally, we actually wanted them to simply include patients only who had a circulating factor, because we figured they're most likely to benefit.

So, we're relatively limited in what data we can collect. They are not, unfortunately, doing the genetic studies. I think that all three of us who are pediatric nephrologists would probably agree that if you have a patient who

presents with FSGS, certainly with certain features, doing genetic testing makes a lot of sense, because some patients probably shouldn't be treated at all. They're not going to get better no matter what you do. And, some patients might do better with certain types of therapy.

Unfortunately, two limitations, number one, is that not everybody really knows a lot about genetic testing. Most people do. They should know this. But, the second problem is that it's not easy to get payment for the genetic testing. So, what we agree with scientifically can't always be duplicated from a reimbursement perspective. So, I, myself, if I had a patient with FSGS, if possible, I'd send off genetic testing. But, not everybody can do that.

But, I think that that's another one of those things that we wanted to have as part of the study but we couldn't quite convince them, and we couldn't quite require it, because it didn't necessarily -- it wasn't necessarily something that would predict outcome and protect safety.

But, it's a good point.

DR. HUDAK: Dr. Hoehn and then Dr. Havens.

DR. HOEHN: I just had a quick comment. It seems really similar to just plasmapheresis with an extra filter in it to take out that cholesterol. So, I just didn't know if there had been any comparison data comparing it in terms of complications and stuff like that, comparing it to plasmapheresis.

I mean, it seems like a similar mechanism, similar risks for clots and embolism and things like that. So, I just didn't know if that was also factored in in terms of comparison for historical controls.

DR. SILVERSTEIN: Absolutely. And, actually, the standard therapy, up to this point, for the treatment -- plasmapheresis for patients who get FSGS before transplant -- so, let me backtrack a little bit to delay all your flights.

So, FSGS develops as a primary disease. In pediatrics it's rarely due to things that you

might see in adults, like hypertension can cause FSGS or FSGS-like features. But, in pediatrics, it's always a primary renal disease. It can occur and then you can go on dialysis or you can get a kidney transplant. And, unfortunately, about 30 to 70 percent of the patients will have a recurrence of the disease after transplant.

The good news is, the outcome after transplant is much better than before transplant. Why? Because, we know when the disease happens. Literally, the patient can be on the operating table, getting a kidney transplant, and protein starts to pour into the urine. It more likely occurs within the first couple of months, but it comes in rip-roaring. You can't miss it. It's different than the primary disease, which is generally more silent and indolent than it is for the recurrence. So, we know when the recurrence happens.

As long as you're watching carefully, you'll know when the recurrence is happening 99 percent of the time. You can jump in right there

and do something. Whereas, you don't have that advantage pre-transplant. Some of these patients could be around for years with a little bit of protein in the urine before they come in, and some of them, by the time they come in it's already past the time where you can give them any kind of therapy.

So, therefore, we have been using plasmapheresis after kidney transplant pretty much the same schedule, 12 treatments in 9 weeks, to treat them. So, the question came up in our mind -- is this better than plasmapheresis. If we're going to approve this before kidney transplant for the primary disease or for those who get a recurrence after kidney transplant, why not plasmapheresis compared to the Liposorber.

Actually, the safety profile for the Liposorber was actually better than it was for the plasmapheresis. So, we were left in a little bit of a dilemma. We're telling people you might want to consider this instead of plasmapheresis. And, we understood that. And, if somebody decides I'm

not going to do it after kidney transplant, I would perfectly understand that. And, I think the sponsor would understand that.

We felt this was a little more specific, that it's removing certain particular factors. Plasmapheresis is a little more broad than that. So, we felt the safety profile was better, but, again, it wasn't our job at the FDA to recommend a therapy. It was our job just to approve this and allow people to decide if they wanted to do it. And, if somebody wanted to do plasmapheresis instead of this, I think everybody would say that's reasonable.

But, the safety profile for plasmapheresis is a little concerning compared to this, so I think the safety profile for this -- especially with the FH data we have in children -- we felt it was reasonable to support the approval of the HDE after kidney transplant.

DR. HUDAK: Dr. Havens.

DR. HAVENS: Peter Havens. Is it within the purview of this part of the FDA to be able to

demand more efficacy data in ongoing studies or at least to understand more data? I mean, you were talking about genetics -- more mechanistic data about why it might not or might not work, given that you're monitoring potential side effects. If you could understand the mechanism and recommend a pill instead of a device, it might benefit the patients dramatically.

DR. SILVERSTEIN: Yes, I agree. The two outcomes we're looking at for probable benefit, so just the terminology we use probably benefit versus efficacy. But, we're getting to the same place.

DR. HAVENS: Right. But, we started today with a great talk, in which Dr. Hertz said, if there's no expectation of efficacy there's no justification of risk. We're talking about risk here. We're talking about unknown efficacy. So, then, the way for us to get to that is to say -- for you to be able to continue to take the risk, you have to be able to justify why this is the most straightforward approach.

DR. SILVERSTEIN: Right. And, we have the constant discussion of what we call benefit-risk. In this case it's probable benefit versus safety. So, just, the terminology is a little bit different, but it's basically the concept you're talking about.

So, the original indications for use that the sponsor proposed was not what was approved. And, the reason for that is we felt exactly as you felt, that you have to identify patients for whom there is no other option. So, these are patients who have reasonably good renal function left.

So, we're not throwing a therapy at a patient who basically is at the end of the road and exposing them to greater risk versus benefit. These are patients who have a GFR of at least 60, which is at least 50 percent of renal function left, and probably greater than that.

So, we felt that they have some renal function to preserve, A, and, B, these are patients in whom they were intolerant of medical

therapy or these are patient who had received the available therapies as standard therapies and weren't responding. So, going back to the indications for you -- so let me go to that. Let's see if I can find it.

So, the indications for use here -- if you look at standard treatment options include a corticosteroid and/or calcineurin inhibitor treatments. Those are the standard therapy. Now, people have used other therapies for FSGS, with very, very variable outcome, and I would say dubious outcome, that is unsuccessful or not well-tolerated.

So, these are patients who basically have no other options. So, we've all been in this situation with our patients, where basically nothing's working or, in whom they're intolerant of the therapy and we have to withdraw the therapy, and we're basically saying, you know what, you have reasonably good kidney function but we've got nothing left for you. So, basically, we'll see you at the end of the road when you're

ready to start dialysis. And, obviously, we follow them along the way, but we're basically saying we have no other place to go.

And, so, I've been in these discussions. The other pediatric nephrologists here have had those discussions. And, it's just that we felt that the probable benefit here is that we can potentially attenuate the progression of the disease and give them more time.

For children, and for the pediatricians here, this is a particular issue, because if you have this disease and you're 8 years old, the earlier the onset of chronic kidney disease and ESRD, the more likely you're going to have problems with growth and development, including cognitive development. And, there are cognitive deficits that occur with patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). So, we felt for many children this is at least giving them some potential option. Now, again, everything with us is a

seesaw of risk versus benefit. Based on the FH data, the children with FH and the safety data from years of this particular device, we know that the risk profile is relatively manageable and actually relatively mild. And, so, we felt that, if anything, what we're seeing is benefit is greater than risk. There's risk, but the benefit is greater.

Now, you raise a good point, I think, and it's a valid point about how are you going to assess efficacy or probable benefit. The two greatest predictors of outcome in any patient with renal disease are your GFR at a diagnosis and the degree of proteinuria. There are other factors that play into this -- blood pressure, et cetera, but the two greatest predictors are your degree of protein in the urine and your GFR at the start. And, those are the ones that we require them to include in this analysis.

So, if you're uncomfortable with the risk-benefit profile here and trying to get your head around it, so were we at the beginning. I should just briefly state -- this submission came in originally, I think, in around 2011 or 2012 and wasn't approved until 2014. Now, there were different reviewers and different groups, but, basically, it went through a lot of people's hands before we eventually approved this.

So, it was one of those things that I can't tell you there wasn't a little hand-wringing on our part, but we felt that, for this patient population in whom there are no options and whom we know they're going to end up at end-stage, we felt we wanted to give them the opportunity to see if this would be helpful.

DR. HUDAK: We have one final comment.

DR. PEIRIS: Very quickly. To answer your fundamental question, Doug did such a fantastic job of clarifying the issues here. Our role in FDA -- we don't evaluation comparative effectiveness -- meaning, if there are other

therapies or other options, that's not specific to the process by our review.

DR. HUDAK: Thank you, Dr. Silverstein. So, despite your worries about being the last, people are literally hanging on every word.

DR. SILVERSTEIN: (Laughs)

DR. HUDAK: So, bring up the last slide and we will do the vote. So, bring up the flashing green lights. And, the question is, does the committee agree with the FDA recommendation to continue surveillance of this device. The record will reflect that we have four people who have had to leave early to catch flight, so we'll start the oral recitation from Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I concur.

DR. DRACKER: Dr. Dracker. I concur.

DR. TOWBIN: Kenneth Towbin. I concur.

DR. HAVENS: Peter Havens. Concur.

DR. CELENTO: Amy Celento. Concur.

DR. WHITE: Michael White. Concur.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. CUNNINGHAM: Melody Cunningham. Concur.

DR. MINK: Jon Mink. Concur.

DR. KASKEL: Rick Kaskel. Concur.

DR. BAKER: Susan Baker. Concur.

DR. WALKER-HARDING: Leslie Walker-Harding. Concur.

DR. HUDAK: Okay. So, we have concluded the day. I would make a couple remarks, and then Skip -- or, do you want to go first?

DR. NELSON: Yes. Let me just make two quick comments. So, first of all, thank you for a long day. And, we realize it was a lot of effort, but we appreciate it. The second is, the meeting in September for the opioids has already been announced. So, as you know, that that's September 15th and 16th, which is a Thursday and Friday. So, those standing members of the PAC will be invited, and then those members who become standing members of the PAC between now and then -- because obviously there are some who are

stepping off that we will then replace -- will be invited to that meeting on Thursday and Friday.

Now, you know we don't expect to keep you over the weekend, so it's easy enough -- even though I can't tell you the date for the safety meeting -- to figure out when it will be. I won't say anything more about that.

DR. HUDAK: Very artfully put. On behalf of the committee, I'd like to thank our colleagues of the FDA for, really, uniformly excellent presentations and a very thorough preparedness to respond to the committee's questions, and note that we've whittled away 13 drugs off whatever the list is, whatever the number was, but there are probably 15 lurking in the wings to replace it as we speak.

And, once again, thank you to Amy Celento and Jonathan Mink and Susan Baker for their terms on the committee. I guess I can note that it's never a never, so there may be some time in the future. All right. Thanks, everybody.

(Whereupon, at 5:17 p.m., the

PROCEEDINGS were adjourned)

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CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the Commonwealth of Virginia

My Commission Expires: November 30, 2016

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