FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE

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MEETING

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THURSDAY
SEPTEMBER 20, 2018

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The Pediatric Advisory Committee met in the Great Room, Building 31 Conference Center, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:50 a.m., Robert Dracker, Chair, presiding.

PRESENT
ROBERT DRACKER, MD, MHA, MBA, CPI, Chair
PREMCHAND ANNE, MD, MBA, MPH, FACC, Voting Member
DAVID CALLAHAN, MD, Voting Member
MARY CATALETTO, MD, FAAP, Voting Member
PEGGY DICAPUA, Temporary Voting Member
RANDALL FLICK, MD, MPH, Voting Member
PETER HAVENS, MD, MS, Voting Member
SARAH HOEHN, MD, MBe, FAAP, Voting Member
BRIDGETTE JONES, MD, MSc, FAAAAI, FAAP Voting Member
JAMES MCGOUGH, MD, Temporary Voting Member
RANDI OSTER, MBA, Voting Member
RONALD PORTMAN, MD, FAAP, Non-Voting Member
WAEL SAYEJ, MD, Voting Member
CHRISTY TURNER, MD, MHS, FAAP, FTOS, Voting Member
KELLY WADE, MD, PhD, Voting Member

ALSO PRESENT

MARIEANN BRILL, MBA, RAC, MT (ASCP), Designated Federal Officer
Susan McCune, MD
Judith Cope, MD, MPH
LCDR Kenneth Quinto, MD, MPH
John Alexander, MD, MPH
Ethan Hausman, MD
Mona Khurana, MD
Amy Taylor, MD, MHS
Steven Bird, PharmD, PhD
Vicky Chan, PharmD
Carmen Cheng, Pharm D
Kate Gelperin, MD, MPH
Ivone Kim, MD
Cindy Kortepeter, PharmD
Robert Levin, MD
Shekhar H. Mehta, PharmD, MS
Courtney Suggs, PharmD, MPH
Peter Waldron, MD
Howard Chazin, MD, MBA
Anthony Fotenos, MD, PhD
Robert Lim, MD
Marc Stone, MD
David Miller
Olanrewaju Okusanya, PharmD, MS

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

8:50 a.m.

CHAIR DRACKER: My name is Bob Dracker. I'm the chairman of the PAC for this coming year. So I'll try to do the best job I can for all of you.

First of all, good morning. I'd like to remind everyone to please silence your cell phones, Smart phones, and any other devices if you haven't already done so. I'd like to identify the FDA press, Gloria Sanchez-Contreras, are you here? Gloria? Oh, thank you very much.

First of all, I just want to remind everyone that there is Internet access. There are slips outside for anyone that hasn't seen that and needs the information. The network is FDA-public, and the password is publicaccess, lower case.

All right. So let's begin. For topics such as those discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal

is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We look forward to a very productive meeting.

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

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

Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

And I'll pass to Marieann to make some more comments on conflicts of interest.

MS. BRILL: Good morning. The following announcement addresses 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 the Pediatric Research Equity Act.

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

The following information on the status of the Advisory Committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at USC Section 208, is being provided to participants at this meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws. Under 18 USC, Section 208, Congress has authorized FDA to grant waivers to special government employees.

And regular government employees have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC, Section 208, their employers.

Those interests may include

investments, consulting, expert witness testimony, contracts, grants, credos, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda includes pediatric focus safety reviews for Intuniv and Lexapro. The FDA will also provide a summary of FDA completed review of pediatric safety issues and updated labeling changes for Exjade. This is a particular matters meeting during which specific matters related to Intuniv, Lexapro, and Exjade will be discussed.

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

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

In order to provide the expert as required to adequately address the topics covered at today's meeting. Dr. McGough and Ms. DiCapua will be participating as temporary voting members. Ms. Peggy DiCapua is participating as the patient family representative which is a voting position.

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

We would like to remind members and temporary voting members that, if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such

involvement. And their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationship that they may have regarding the topics that could be affected by the Committee discussions. Thank you.

CHAIR DRACKER: Thank you, Marieann. I'd like to go around the table now and greet each of the members and FDA representatives. Please state your name, your involvement, and location of origin. Thank you. We can start with you.

MEMBER JONES: Good morning, my name is Bridgette Jones. I am from Children's Mercy Hospital in Kansas City. I'm the pediatric healthcare representative from the AAP.

MEMBER FLICK: Randall Flick, pediatric anesthesia, Mayo Clinic, Rochester, Minnesota, member of the Committee, new member of the Committee.

MEMBER SAYEJ: Wael Sayej, pediatric

gastroenterologist from Connecticut Children's Medical Center and the University of Connecticut School of Medicine. This is my third year on the Committee.

MEMBER TURER: Christy Turer. I'm both internal medicine and pediatrics. And I've been on the Committee, I guess, since 2014. And I'm at UT Southwestern Medical Center in Dallas.

MEMBER OSTER: I'm Randi Oster. I am the consumer representative for the Committee. This is my first time. I'm from Fairfield, Connecticut.

MEMBER WADE: Kelly Wade, member of the PAC. I'm a neonatologist from Children's Hospital of Philadelphia. And I've been on the Committee for a few years.

MEMBER CATALETTO: My name is Mary Cataletto. I'm a pediatric pulmonologist at NYU Winthrop in New York and a member of the PAC.

MEMBER DICAPUA: Peggy DiCapua, I'm a temporary patient representative, first meeting, from Dyer, Indiana.

MEMBER ANNE: Premchand Anne, pediatric cardiology. I'm from Ascension St. John Hospital and Wayne State University School of Medicine, Detroit, Michigan. And this is my first meeting as a new member.

MEMBER CALLAHAN: David Callahan. I'm a child neurologist with Washington University in St. Louis. This is my second year on the Committee.

MS. BRILL: I'm Marieann Brill. I'm the designated federal officer for the PAC.

CHAIR DRACKER: I'm Bob Dracker, Chairman of the PAC. I'm pediatrics, hematology, and blood banking. I was a consultant for four years and a member now. This is my fifth year. And they'll probably kick me off after this year anyway. But it's a pleasure being here with all of you. I'm from Syracuse, New York. Thank you.

MEMBER MCGOUGH: James McGough. I'm a child and adolescent psychiatrist from UCLA and a temporary voting member today.

MEMBER HOEHN: Sarah Hoehn. I am

pediatric ICU and pediatric palliative care at the University of Chicago. I'm a member of the PAC for a little while. I'm not sure how long.

MEMBER HAVENS: Peter Havens, I'm a pediatric infectious diseases specialist at the Medical College of Wisconsin in Milwaukee and a member of the PAC.

DR. COPE: Judy Cope, pediatrician and epidemiologist. And I'm the Safety Team lead at the Office of Pediatric Therapeutics.

MS. MCCUNE: I'm Susan McCune. I'm the director of the Office of Pediatric Therapeutics, and my background is I'm a neonatologist.

LCDR QUINTO: Ken Quinto, I'm a medical officer in the Office of Pediatric Therapeutics at FDA. I am a pediatrician and trained in allergy and immunology as well.

DR. HAUSMAN: Ethan Hausman. I'm from the Division of Pediatric and Maternal Health. My training's in pediatrics, pathology, transfusion medicine, and blood banking.

DR. ALEXANDER: My name is John Alexander. I'm the deputy director of the Division of Pediatrics and Maternal Health. My training's in pediatrics and infectious disease.

DR. KIM: My name's Ivone Kim. I'm a pediatrician. I'm a medical officer in the Office of Surveillance and Epidemiology.

DR. LEVIN: Hi, my name is Bob Levin. I'm a lead medical officer in the Division of Pharmacovigilance. And my background is in psychiatry.

CHAIR DRACKER: Dr. Portman, if you can introduce yourself, please?

MEMBER PORTMAN: I'm Dr. Ron Portman. I'm with Novartis Pharmaceuticals and a member of the PAC, non-voting. And I'm a pediatric nephrologist.

CHAIR DRACKER: Thank you all for being here with us. We will now proceed with opening remarks from Dr. Susan McCune, Director of the Office of Pediatric Therapeutics.

MS. MCCUNE: Good morning all. Thank

you for coming today. I really appreciate it. I am Susan McCune. You just heard me introduce myself. And I'm the director of the Office of Pediatric Therapeutics. You all are used to seeing Skip Nelson here in this role. Unfortunately, Skip decided to leave us and go to J&J as of December of last year.

And so we have some --- first I want to start with some personnel updates and then tell you about a couple of issues before we get going today.

So the first I want to say is since Skip left I have had the opportunity to hire Dr. Dionna Green who is right there on the end -- wave, Dionna -- who is now the Deputy in the Office of Pediatric Therapeutics.

Dr. Green joined OPT this summer as the deputy from the Office of Clinical Pharmacology and the Office of Translational Sciences in CDER where she was the lead for policy and guidance.

She received her medical degree from

Howard University College of Medicine in Washington, D.C., and completed residency in pediatrics at the Herman and Walter Samuelson Children's Hospital at Sinai in Baltimore, did her clinical pharmacology research fellowship at Georgetown, and was an FDA Commissioners Fellow prior to joining the Office of Clinical Pharmacology. And I am very pleased to have Dr. Green joining us in the Office of Pediatric Therapeutics.

I also wanted to take a moment to introduce a couple of the new members of the Committee, as you've heard today. While Dr. Dracker is not new to the Committee, he is certainly new as our chairperson. I wanted to give you a little background on him.

He's the clinical associate professor in the Departments of Pathology and Pediatrics at SUNY Health Science Center at Syracuse in Syracuse, New York. He's the owner and medical director of Summerwood Pediatrics and founder and medical director of Infusacare Medical Services,

Liverpool, New York.

Dr. Dracker is Board certified in pediatrics, a practicing pediatrician in Summerwood. He received his MD from SUNY Health Science Center in Syracuse, New York, and completed his residency in pediatrics and fellowships in hematology, oncology, and blood banking transfusion medicine at SUNY Health Science Center.

As I said, he's been a member of the Pediatric Advisory Committee for four years. And today, we welcome him as the chair of our Committee.

Dr. Randal Flick introduced himself. He is the professor of anesthesia and pediatrics at Mayo Clinic College of Medicine and Science and director of the Mayo Clinic Children's Center in Rochester, Minnesota.

Dr. Flick's recent research has centered on risk assessment for various aspects of pediatric anesthesia practice, including cardiac arrest, laryngospasm, malignant

hypothermia, aspiration, and anesthetic toxicity.

Dr. Flick's current primary area of research centers on the effects of anesthetic exposure on the developing brain. He earned his MD from the University of North Dakota Medical School and did his residency in pediatrics at St. Louis Children's Hospital, Washington University, in St. Louis, and has an advanced specialty training in pediatric anesthesia and intensive care at John's Hopkins Hospital.

Dr. Flick is Board certified in pediatric anesthesiology and pediatric clinical care medicine. He's authored many articles and book chapters on pediatric anesthesiology. In the past, he has served on the FDA Anesthetic and Analgesic Drug Products Advisory Committee and is currently a new member to the PAC. And we would like to welcome him.

And Randi Oster is the Pediatric Advisory Committee newly appointed consumer representative. She is the CEO and co-founder of Help Me Health in Fairfield, Connecticut, since

2012 and brings immense knowledge of the healthcare system.

Additionally, she is the multi-award winning author for her book, "Questioning Protocol," and advocates for culture change in the hospital setting with improvement in patient experiences and outcomes at the forefront.

Ms. Oster received her MBA from Boston University and BS in Electrical Engineering from Union College. She was recognized as a finalist in Women of Innovation at the Connecticut Technology Council in 2018 and was previously an aerospace program manager at General Electric with a focus on aircraft safety. We look forward to having her join us on the PAC.

The second update I wanted to give you, I don't know how many of you are aware of this, it's called the STRIDER trial. And I would have put out what it stood for, except I kind of couldn't figure out all of the --- where the acronym kind of came from. And I'll let you all try to work it out. It is the Sildenafil Therapy

in Dismal Prognosis Early-onset Fetal Growth Restriction. I'm not sure how you get STRIDER out of that, but just so you're aware.

The STRIDER trial protocol was published in 2017. This is an international consortium of randomized placebo control trials in New Zealand, Australia, Canada, Ireland, the Netherlands, and the UK.

The results of the UK trial were published in February 2018 and reported that Sildenafil did not prolong pregnancy or improve pregnancy outcomes in severe early-onset fetal growth restriction.

There were eight serious adverse events reported during the course of the study, six in the placebo group and two in the Sildenafil group. And the fetal and neonatal deaths did not differ between the groups. There were a total of 135 participants in that trial.

In July of 2018, there was a report in the press that the Dutch arm of the trial had been put on hold following the deaths of 11

babies possibly due to, quote, "a new lung condition," or "a related lung condition," sorry.

In that study, there were 90 treated patients and 90 placebo --- 90 treated mothers and 90 placebo mothers. In the treated group, more babies were born with lung problems than expected. And 11 of those babies died in addition to eight babies that died of other causes. In the control group, three babies developed lung problems, and nine died of other causes.

The trial is currently on hold at all the sites. And the data from all the sites are being analyzed and will be reported out when they have completed the analysis. I just wanted you all to be aware of that study.

And then I wanted to update you on the Advancing the Development of Pediatric Therapeutics ADEPT 5 Workshop that we held last Friday, September 14th. This is the fifth workshop in the series. And this year we discussed pediatric pharmacovigilance.

We had a number of talks about current approaches to pharmacovigilance followed by future directions involving large databases, electronic health records, and even social media. We will be discussing internally how we might augment the pediatric safety information that we bring to the PAC in the future.

And then I am required to discuss the non-compliance letters. In the Center for Biologics and Research there are two non-compliance letters. This is the link. There are no new compliance letters since the last time I reported these to you.

In the Center for Drug Evaluation and Research, there are 30 non-compliance letters that are posted. There are two additional letters that have been posted since the last time I reported. So the last time there were 28. This time there are 30.

The websites list the sponsor product, a copy of the non-compliance letter, the sponsor's response if available, and the status

of the PREA requirement, for example, whether it was released, replaced, or fulfilled. And that concludes my introduction.

CHAIR DRACKER: Thank you, Dr. McCune. We will now have Dr. Judith Cope, Safety Team Leader, provide updates for the Office of Pediatric Therapeutics.

DR. COPE: So good morning, and welcome, and thanks for everybody in attendance. And we look forward to your participation in our meeting today.

What we really wanted to do was to just give you two brief updates that we thought were really important to let you know about. One is on montelukast and the other is on Noxafil.

So I'm going to start off with montelukast which I'm sure you all know is used for prophylaxis and chronic treatment of asthma, seasonal allergic rhinitis, and perennial allergic rhinitis, and the prevention of exercise-induced bronchoconstriction. And I've put the age groups there, so you'll see they all

are different for the pediatric age group approval.

Now, the neuropsych events have been very important. In fact, I think there were some of you that were actually at the Pediatric Advisory Committee back at the end of 2015. And there were a lot of neuropsych events.

And the PAC, your input was very important at that point, because there was a lot of discussion about, well, maybe the label should be putting things in there about the warning and precautions about neuropsych events, and things like contacting your healthcare provider, you know, and stopping it before, you know, things get worse, et cetera.

So there was a label change that happened the following year, in December of 2016. And important information on the neuropsych events was put into the warnings and precautions, the adverse reaction section, and also in the part of the label that is the patient counseling information on how parents should handle stuff

and definitely contacting their healthcare provider.

Now since that time, FDA has gotten a lot of neuropsych events. And basically, this has really seemed to be an important safety issue that needed further evaluation by FDA, not just pharmacovigilance looking at the FDA adverse events that are submitted but also extending it to look extensively at the published literature, clinical trial data that's new and old, and pulling this together to update things, as well as using the Sentinel database to do further analysis, update things, and really do a thorough review.

And the plan is to report this back to the PAC. It's anticipated that we will do that in 2019 with the full review and the focus again on the neuropsych events. So you should be hearing about that in a year. And your input, again, is going to be very important.

The other brief update is on Noxafil. Noxafil had its first mandated pediatric safety

review presented to the PAC about two and a half years ago. And at that time, the PAC was informed that there were problems going on with drug interaction of posaconazole and vincristine.

And there was going to be a labeling change and, you know, that we would get back to you about that. So that's what I'm doing here.

I just want you to know there was a labeling change in September of 2016. And the sections that put in about this drug/drug interaction was in the warning and precautions. There's a specific subsection on vincristine toxicity, and also in drug interactions and a special subsection update.

Now, I wanted to also just put out there that there was an additional labeling change of putting pancreatitis in the adverse reaction section. And again, it was listed as a less common adverse event, but it was put into the label.

And I might just mention, actually, if you go back in time, or you may recall, there was

one or two --- there was one case of pancreatitis. But as FDA had looked at adults and kids, this was felt to be added.

Also want to mention that Noxafil had another pediatric labeling change that mandated another safety review. And that was completed a few months ago. And there were no safety issues that arose that FDA had any concerns about. It thought the label was appropriate. And so that actually is web-posted. But just wanted to update you on that follow-up. And that's it.

CHAIR DRACKER: Thank you, Judith. We will now begin the open public hearing period. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure that such transparency at the public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages

you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship you might have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee place great importance in this open public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many

instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chairperson. Thank you for your cooperation.

Will Speaker Number 1 please stand up?

DR. SRINIVASAN: Good morning.

CHAIR DRACKER: Thank you.

DR. SRINIVASAN: Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a Master's in Public Health from Johns Hopkins University. I'm a senior fellow with the National Center for Health Research which analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers.

We do not accept funding from drug and

medical device companies, so I have no conflicts of interest.

I have strong concerns about the safety of two drugs in question today. In regards to Lexapro, we appreciate the fact that the FDA continues to look at adverse events, because the rate of drug prescription has doubled in past six years.

First and foremost, we are concerned that the safety study will be used to justify advertising for use in 7 to 11 year olds without evidence that it works. A very short summary of the safety study is not adequate to fully evaluate the results. More information should be provided to the Committee.

In addition, there is limited evidence that the drug works in adolescents. This is very concerning, considering that two or three studies done in 7 to 17 year olds do not show the drug to be efficacious in younger children.

Clearly, there are psychiatric risks with Lexapro for children. And yet there is no

clear evidence of the benefit. Using the FAERS to determine the incidence of new or increased adverse reactions is inadequate, given the well-known problem of under-reporting.

Our bottom line is that the FDA has not provided the Advisory Committee with adequate information for you to conclude that the benefits outweigh the risks for children ages 7 to 11. Lexapro should not be approved for safe and continued use in children under 12.

There are also serious questions about whether its benefits outweigh the risks for adolescents as well. More research is needed, and the research carefully be reviewed by the FDA and by this Advisory Committee.

In regards to the drug prescribed for ADHD, Intuniv: Intuniv has very serious psychiatric adverse events reported to the FDA's FAERS. FAERS can't tell us how much of a risk, suicidal ideation, homicidal ideation, and aggression are for this drug.

Although the number of these adverse

events are small in the data provided by the sponsor, it is important to question whether the benefits outweigh the risk, given that other treatments are available for ADHD.

At the very least, these risks need to be prominently included in a black box warning on the label so that parents can make informed decisions about their child's potential use of this drug.

This Advisory Committee has an essential role in protecting children from drugs that may be unsafe or unproven for children. We urge you to urge the FDA to demand better data and require better warnings on labels. Thank you.

CHAIR DRACKER: Thank you very much. Are there any other comments from the public?

Just to explain how we'll proceed now, the open public hearing period extends for an hour from the start of it. We will proceed with our meeting. And if there are public comments in the meantime, please raise your hand, and I will

acknowledge you so we can do so.

There was also somewhat of a change in the process that we're going to do. We're going to discuss Lexapro, then there'll be a discussion of generic drugs, and it'll go back to comments regarding Lexapro.

Both the Food and Drug Administration and the public believe in the transparent process for information gathering and decision making. To ensure such transparency at the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants to advise the Committee of any financial relationship that they may have with the firms at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the

Committee if you do not have any such financial relationship. If you choose not to address the issue of financial relationship at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the FDA presentation.

CDR SUGGS: Good morning. My name is Courtney Suggs. I'm a safety evaluator in the Division of Pharmacovigilance, Office of Surveillance and Epidemiology.

The pediatric focus safety review I'm going to present today is on escitalopram. Of note, this product was previously presented to the PAC in 2011.

This is the outline of what I'll be discussing this morning. We'll start with background information followed by the Pediatric Research Equity Act studies, relevant pediatric labeling, drug use trends, adverse events, and finally we'll conclude with a summary.

Escitalopram or Lexapro was originally

approved in 2002. It is a selective serotonin reuptake inhibitor. It is indicated for the treatment of major depressive disorder in adults and adolescents and for the treatment of generalized anxiety disorder in adults.

The dose varies by indication. For MDD, the initial and recommended dose is 10 milligrams per day. The maximum dose is 20 milligrams per day. For GAD, for generalized anxiety disorder, the initial and recommended dose is 10 milligrams per day, and there is no maximum label dose. Escitalopram is available as a tablet and as an oral solution. And the sponsor is Forest Labs.

There was a previous pediatric labeling change in 2009. The safety and efficacy were established in adolescents 12 to 17 years old for the treatment of MDD. Maintenance of efficacy was supported from extrapolation of data from adult studies along with comparisons with racemic citalopram pharmacokinetic parameters in adults and adolescents.

As I previously stated, this product was presented to the PAC in 2011 because of this labeling change. The DPV review, in association with this labeling change, did not recommend any labeling changes at that time and recommended to continue routine pharmacovigilance monitoring.

The Committee agreed and highlighted the difficulty of conducting studies in various subgroups of the pediatric population.

An open label, long term study of escitalopram to evaluate the safety and tolerability in children 7 to 11 years old with MDD was conducted. This was the study that triggered this review and presentation.

It was a 26-week flexible dose, multi-center study involving 16 centers in the US. There was a one-week, no drug screening period and a flexible dose treatment period for 24 weeks followed by a two-week taper down period.

The starting dose was ten milligrams per day, and dosage was to be increased to 20 milligrams per day at the end of Week 4 in the

absence of an adverse reaction and based on the investigator's judgement.

One hundred and sixty-five patients were enrolled, and the population consisted of 108 --- the safety population included 118 patients consisting of all patients enrolled in the study who took at least one dose of escitalopram.

There was no formal statistical efficacy analysis conducted and the safety and effectiveness of escitalopram for the treatment of MDD in patients younger than 12 have not been established.

The primary safety end-point of this study included adverse events recording, physical examination, clinical laboratory evaluations, electrocardiograms, vital signs, and the Columbia Suicide Severity Rating Scale.

No deaths were reported. Two patients, or 1.7 percent, reported serious adverse events. These included mania and suicidal ideation, each in one patient. Nine

patients or 7.6 percent reported adverse events that led to discontinuation. And the most frequent cause of discontinuation by system organ class was psychiatric disorder that occurred in seven patients or 5.9 percent.

Seventy-five percent of patients reported a treatment emergent adverse event during the open label period. The most common were gastrointestinal, followed by nervous system disorders, and most were mild in severity.

Overall, escitalopram was well tolerated, and there was no new pattern of adverse events and no new safety concerns in the pediatric population.

Over the next few slides, we'll discuss escitalopram labeling. The box warning we all know well. It includes an increased risk of suicidal thinking and behavior in children, adolescents, and young adults who take antidepressants. It underscores the need for monitoring for the worsening and emergence of suicidal thoughts and behavior.

In Section 2 here, I've listed only the section that applies to pediatric patients. These doses were for adolescents with MDD and were previously mentioned.

Section 5 includes a list of warnings and precautions. The only warning and precaution that directly mentions children is the clinical worsening of suicide risk in Section 5.1. This supports what's in the boxed warning.

Other warnings and precautions could also include pediatric patients. And I've listed them here. These warnings and precautions are associated with other SSRIs also.

Section 6.1, clinical trials experience, addresses commonly observed adverse actions. Information on pediatric adverse events came from 576 pediatric patients with MDD. The safety and effectiveness in pediatric patients less than 12 years old has not been established.

Adverse events associated with discontinuation occurred in 3.5 percent of pediatric patients receiving escitalopram and 1%

of patients receiving placebo. Insomnia was the most common adverse event associated with discontinuation.

This is a continuation of the last slide. And overall, the profile of adverse events in the pediatric population was similar to what we see in adults, back pain, urinary tract infection, vomiting, and nasal congestion were reported to occur in at least two percent of pediatric patients and greater than placebo.

Section 8 and Section 12 of the labeling describes the use in special populations under clinical pharmacology. As I previously stated, the safety and effectiveness of escitalopram in pediatric patients less than 12 years old with MDD has not been established. And this is the study that triggered this review.

Decreased appetite and weight loss have been observed in association with the use of SSRIs. And the label recommends regular monitoring of weight and growth in children and adolescents taking an SSRI.

Section 12 describes the pharmacokinetics in adolescents. In a single-dose study of escitalopram, 10 milligrams, the AUC decreased by 19%, and the Cmax increased by 26 percent in healthy adolescents compared to adults.

The escitalopram half-life steady-state Cmax and AUC were similar in adolescents taking escitalopram compared to adults. And no dosage change is recommended in the adolescent patients.

This is a slide that describes the study used to gain the indication for the treatment of MDD in adolescents 12 to 17 years old. These studies initiated the previous pediatric focus safety review and PAC presentation.

It showed statistically significant greater mean improvement from baseline compared to placebo on the CDRS-R. Positive results from this study largely came from the adolescent subgroup.

This is a continuation of the last slide and describes two studies that did not demonstrate the efficacy of escitalopram in children or adolescents. Both are flexible dose, placebo controlled MDD studies. One was an escitalopram in patients 7 to 11 years old, and one study involved escitalopram in adolescents.

The maintenance of efficacy in escitalopram has not been studied, but can be extrapolated from the adult data as well as by comparisons of escitalopram pharmacokinetics in adults and adolescents.

This figure provides the nationally estimated number of patients who received a dispensed prescription for escitalopram from US outpatient retail pharmacies from April 2011 through March of 2017 annually.

Overall, the number of patients who received a dispensed prescription for escitalopram increased from approximately 4.3 million in the 12-month period ending March 12, March of 2012, to 7.2 million in the 12-month

period ending March of 2017.

Pediatric patients zero to 16 years old accounted for approximately three to four percent of the total patients annually over the estimated time period and nearly doubled from approximately 148,500 patients to 290,000 pediatric patients during the study period. I've highlighted this pediatric data in yellow.

So for our review, we reviewed 645 pediatric reports with a serious outcome. Of these, 74 reported the outcome of death. We excluded 633 cases, including the 74 deaths. The 463 transplacental or breast feeding patients were reviewed but excluded.

There is a pregnancy registry for anti-depressants run by the Massachusetts General Hospital. This may account for some of the large numbers of cases. Additionally, some of these cases reported birth defects and some were coded as transplacental exposure without an adverse event reported.

According to the CDC, birth defects

affect about three percent of all babies born. And this has been steady over the last several decades. Birth defects are the leading cause of infant death, and they account for about 20 percent of all infant deaths.

We also excluded 72 foreign cases. We reviewed these cases but did not identify any new potential signals. We also excluded duplicate cases, cases of multi-drug overdoses, cases with insufficient information, cases that did not report the use of escitalopram in a pediatric patient, and cases in which the patient was not reported to have taken escitalopram.

The deaths included either transfrontal exposure, completed suicide, which is a labeled event, or multi-drug overdose. Thus, our pediatric case series involved 12 pediatric patients.

This slide gives you an overview of the cases we included in our pediatric case series. There are three male and nine female patients. The majority of the patients were

adolescents, 12 to less than 17 years of age. One case reported a hospitalization, one reported a disability, and ten cases reported an other serious outcome. And as I mentioned, there were no deaths in our case series.

This is a summary of the 12 cases in our case series. There were five lack of efficacy, four homicidal ideations, and one each Chronic Fatigue Syndrome, Postural Orthostatic Tachycardia Syndrome, non-alcoholic steatohepatitis, and neuromuscular instability. And of note, there was no discernible pattern for the previously unlabeled adverse events.

These describe the lack of efficacy cases. All were direct reports from consumers or non-healthcare professionals, and most lacked clinical information.

There was an 11-year old male previously well maintained on both Lexapro and Abilify for MDD and GAD. His depressive symptoms returned within three days of receiving a new Lexapro prescription, and these worsened over the

next two weeks up to and including suicidal ideation.

Lot numbers were requested but were unavailable from the pharmacy. The reporters say that the pharmacy said they have had no other complaints.

There was another 11-year old who stated they, quote, "become depressed with anything but brand." There was a 14-year old who experienced a, quote, "increase in depression with generic and also some nausea."

There was a 15-year old who refilled escitalopram with a new generic version and developed anxiety and behavioral dysregulation similar to what she exhibited prior to treatment. And her symptoms improved significantly with brand Lexapro. And this was the only case out of the five that included any tablet identifying information.

Finally, there was a 16-year old with a history of bipolar disorder who switched from brand to generic due to insurance and went manic

within two days and had violent outbursts, mood swings, and insomnia. She switched back to brand and felt better within three days.

Doctors Kortepeter and Chazin will present more on this later. And we ask you to please hold your questions on this topic until after their presentations.

This slide summarizes the four homicidal ideation cases. Two cases lacked clinical information to enable us to make an assessment. The 16-year old male experienced homicidal ideation after switching from brand to generic. The 17-year old female experienced homicidal ideation after experiencing a shooting at her school.

In these two cases, escitalopram was being used off-label for obsessive compulsive disorder in one case, and the indication was not reported in the other case.

The last two cases included psychiatric patients with complicated histories, including PTSD and Oppositional Defiant Disorder.

These patients were also reported to be non-compliant with their medication regimens and their medical appointments.

In conclusion, this completes our presentation about the escitalopram focused pediatric safety review. We concluded there are no new safety signals that were identified, and the Agency recommends continuing ongoing post-market safety monitoring if the Committee concurs.

Finally, we would like the Committee's input into whether pediatric focused safety reviews, such as the one I just presented, without new risks of potential safety signals should be posted on the Web in the future.

Again, please hold your questions until Doctors Kortepeter and Chazin present. And we will post these two summary slides at the conclusion of their presentation for comments or questions.

And finally, I would like to acknowledge the people who assisted with this

review and presentation, listed on the slide. Thank you.

CHAIR DRACKER: Thank you, Courtney. We're going to discuss generic drugs next. As you can see with some of this data, discussion of generic drugs is important.

I know personally I experienced a lot of difficulties with children on various psychotropics or other ADHD medications in which they claim they notice a significant difference in branding versus generics, which also affects their insurance.

So in that vein~~vain~~, we will only discuss the presentations provided to us which included an overview of the FDA Adverse Reporting System, and lack of efficacy and generic drug approval process, and discussion on trade versus generic drugs. There will be no discussions of individual sponsors, firms, and drugs with a generic, or brand, or drug class. Thank you.

Dr. Kortepeter?

DR. KORTEPETER: Good morning. My

name is Cindy Kortepeter, and I'm the director of the Division of Pharmacovigilance within the Office of Surveillance Epidemiology here at the FDA.

You've just heard the previous presenter mention that 5 of the 12 cases in the Lexapro case series were reports of lack of effect. More specifically, they were cases of product substitution and product quality issues.

We recently completed a study on reports of drug ineffective, reports from FAERS. So we thought that this will be a good opportunity for us to give an overview on our experience with Drug Ineffective Post-marketing Reports and drug safety surveillance. I will be using the terms lack of effect and drug ineffective synonymously throughout this presentation.

Here's an outline of the presentation. I will begin by providing background information on spontaneous adverse event reports and the FDA Adverse Events Reporting System database, as well

as background on reports of drug ineffective in the database.

I will then describe a recent study we conducted on Adverse Event Reports of drug ineffective and include our findings and general conclusions.

Most of you are probably familiar with this slide on how safety reports get to the FDA. Our spontaneous Adverse Event Reporting System is set up so that anyone can report a suspected adverse event.

Anyone including patients, consumers, and healthcare professionals can report voluntarily adverse events either directly to the FDA via the MedWatch program, as shown on the left-hand side of the slide, or they can report voluntarily to the manufacturer which is shown on the right. The manufacturer, under the Code of Federal Regulations, is then required to submit all adverse event reports they've received to the FDA.

Regardless of how FDA receives these

reports, whether it's the five percent that we get from direct reporting or the 95 percent that's submitted by the manufacturers, the reports end up in the FDA Adverse Event Reporting System which is also known as the FAERS database.

The FDA Adverse Event Reporting System, or FAERS, is a computerized database containing spontaneous adverse event reports for human drugs and therapeutic biological products.

Currently, there are more than 14 million reports in the system with the earliest reports dating back to 1968. Last year alone, in 2017, more than 1.8 million reports were entered into the database.

The number of reports entered in the FAERS database has been increasing over the years. This bar graph depicts the uptick over the past 11 years with all report types increasing. The different report types consist of direct reports, shown in red, as well as reports from manufacturers.

The manufacturers are required to

submit reports of serious, unlabeled events within 15 days, which we call 15-day or expedited reports, and that's shown in blue. And all other events are reported on a periodic basis, which is currently quarterly for the first three years after approval then annually thereafter. And that is shown in green.

So what are people reporting? The reported adverse events are coded using the Medical Dictionary for Regulatory Activity, or MEDRA, terminology at the preferred term or PT Level.

This table shows the most frequently reported adverse events in the FAERS database. As expected, the top of the list contains events associated with common complaints, such as nausea, vomiting, headache, fatigue, diarrhea. But the number one event, consisting over 650,000 reports, or nearly 6 percent of all reports in the database, is drug ineffective.

Now, not all regulatory authorities in other countries consider lack of effect or drug

ineffective as a reportable adverse event.

In the United States where Code of Federal Regulations, under 21 CFR 314.80, defines adverse drug experience as an adverse event occurring in professional practice from a drug overdose, from drug abuse, from drug withdrawal and, as highlighted in red, any failure of expected pharmacological action. In other words, lack of effect or drug ineffective is a reportable adverse event in the United States.

So now I'll describe the study we recently performed to evaluate the post-market reports of drug ineffective in the FAERS database.

As I've already mentioned, the most commonly reported adverse event based on frequency of MEDRA preferred terms in FAERS is drug ineffective.

Drug ineffective reports in FAERS have not been assessed systematically for quality and influential value from a pharmacovigilance perspective. So the objective of the study was

to describe the drug ineffective reports in FAERS and provide data to support recommendations on how best to evaluate these reports.

What we did was we searched the FAERS database for all reports received by the FDA for a four-year period from September 2012 through August of 2016. The retrieved reports were stratified by those coded with the MEDRA preferred term, drug ineffective, and without the MEDRA preferred term, drug ineffective.

Then we conducted a manual evaluation of a subset of FAERS reports to determine the usefulness of the reports from a pharmacovigilance perspective.

We defined useful as reports containing the necessary information that would prompt a reviewer to consider action which, in most cases, would be obtaining additional information. For this study, a useful report contains Criteria 1 and 2 and at least one of the other four criteria listed in the table.

In other words, a report was

determined to be useful if the suspect product associated with the complaint of ineffectiveness was clearly identified, and the narrative in the report contained enough information to support the complaint of ineffectiveness, and at least one of the following four criteria was present.

The report contained MEDRA terms beyond drug ineffective. The suspect products batch or lot number was recorded. A beneficial response prior to the administration of the suspect product was recorded, or if it was reported that medication switching occurred, such as a switch from a brand to a generic or a generic to another generic product.

So this slide of results takes you from the big number down to the little number. So for the big number, we found that over 3.8 million reports were entered into the database over the four-year study period.

Of those, nearly 250,000 reports were coded with the preferred term, drug ineffective. From the 250,000 reports, we performed a manual

review of 552 reports and determined that 43 of the 552 were deemed useful. The sample size of 552 were calculated by our statistician who took into account a prevalence rate as well as the precision of drug ineffective reports with potential utility.

Now please bear with me through the next few slides. They're quite busy, so don't try to read them. But I will call attention to the key points which will be highlighted with red rectangles.

This slide compares the approximately 250,000 drug ineffective reports to the 3.6 million non-drug ineffective reports during the study period.

Now, reporters are usually classified as healthcare providers or consumers. When comparing the reporter type between the drug ineffective reports and the non-drug ineffective reports, we noted that more consumers submitted reports of drug ineffective while the non-drug ineffective reports were submitted by nearly

equal numbers of consumers versus healthcare professionals.

And while age distributions were relatively similar between the drug ineffective and non-drug ineffective report groups, the drug ineffective reports were more often missing the patient's age.

Outcomes are often captured in the reports. A serious outcome is one in which the reporter believes the adverse event contributed to a hospital admission, or a prolonged stay in the hospital if the patient was already an inpatient, or if an adverse event contributed a death, a disability, a life-threatening event, a congenital anomaly or an important medical event such as requiring medical or surgical intervention.

We noted that the majority of the drug ineffective reports from our study had non-serious outcomes. And from our manual review of the subset of 552 reports, we found that three-quarters, or 75 percent of the reports involved

brand name products. Most, 94 percent, did not indicate that the ineffectiveness was from switching. And most did not describe having a prior beneficial response to the product.

In other words, most of the reports lacked clinical details needed to help us distinguish drug ineffectiveness from disease progression.

As mentioned earlier, from the manual review of the 552 reports we deemed 43 of the reports as useful. Those reports contained some of the necessary information that would prompt a reviewer to consider further action, such as obtaining additional information.

What was different in these 43 useful reports was that about half involved generic products, whereas the sample of the 552 subset from the previous slide showed that 75 percent implicated a brand name product.

Also in the 43 useful reports, switching, such as from brand to brand, excuse me, from brand to generic, or generic to generic,

or generic to brand was involved, and nearly half reported a prior beneficial response to the suspect product.

More importantly, many more of the useful reports included a lot number or a batch number for the suspect product, and additional preferred terms, beyond just drug ineffective, were provided with product quality and product substitution issues as the top two additional preferred terms.

Findings from the study include the majority of drug ineffective reports did not report a serious outcome. They were more likely to be reported by consumers, and the suspect products were primarily used for the management of symptomatic conditions, suggesting that consumers have self-awareness of worsening or no improvement of their own subjective experiences.

A higher proportion of the suspect products were identified as generic in the reports deemed useful compared to the proportion of drug ineffective reports sampled during the

study period.

We acknowledge some limitations to the study. We did not capture all the potential reports describing drug ineffectiveness. And although we determined the sample size needed to accurately estimate the proportion of drug ineffective reports considered useful, our resulting sample of useful cases limits the generalizability of the specific characteristics within the subset.

And finally, our definition of useful was based on the expertise of reviewers with pharmacovigilance experience which may limit reproducibility.

In conclusion, in the useful reports, generic products tend to be reported as a suspect product more frequently. But useful reports are often accompanied with the preferred terms, product quality issue or product substitution issue. And information about medication switching or information on batch or lot numbers can be useful.

In short our study, which has since been published, showed an overwhelming majority of reports of drug ineffectiveness occurring without switching and that the product didn't meet the patient's expectation of effectiveness.

We know from clinical trials that there is variable efficacy. The consumers have different expectations. Our study also found that the overwhelming majority of drug ineffective reports were not useful from a pharmacovigilance perspective.

So bringing this back to the Lexapro cases of lack of effect, when concerns arise with drug ineffectiveness when switching to a generic product, we will work closely with our counterparts in the Office of Generic Drugs.

Our next speaker, Dr. Howard Chazin, from the Office of Generic Drugs, will give an overview of how generic products are approved and how we work together on safety issues that arise specifically for generic products.

I'd like to acknowledge my colleagues

on the slide who collaborated on the drug ineffective study and publication. Thank you.

CHAIR DRACKER: Thank you, Cindy. Dr. Chazin?

DR. CHAZIN: Hello, my name is Dr. Howard Chazin, and I'm the director of the Clinical Safety Surveillance staff in the Office of Generic Drugs. We're a small interdisciplinary staff of reviewers tasked with ensuring the safety of generic drugs, generally, to give you an overview of generic drug development and the safety evaluation of generic drugs.

So here's my outline. First, I'll discuss the basic generic drug approvals, then highlight the differences between the contents of what we call an abbreviated new drug application compared to an NDA or new drug application.

I'll then discuss the framework for generic drug development, and that will lead me into the focus on generic drug safety surveillance. First, you need to kind of know

some basic information in order to frame the presentation.

FDA, as you know, has a lot of acronyms, and for listeners who are not familiar with FDA's usage of these, I'll try to spell them out frequently as I go through my talk.

The approval of a generic drug relies on information from the innovator or brand name drug. This is often called the reference listed drug. An abbreviated new drug application, which we call and ANDA, relies on FDA's findings of safety and effectiveness from the reference listed drug during both investigational new drug investigations and new drug application phases of drug review.

And a generic drug requires demonstration of sameness of a number of characteristics and some additional information to promote reliance on the data in the new drug application.

The regulatory basis for FDA's ability to streamline and therefore abbreviate generic

drug approvals reaches back to the Drug Price Competition and Patent Term Restoration Act of 1984, also known more commonly as the Hatch-Waxman Amendments to the Food and Drug and Cosmetic Act.

This allowed for the basic scheme of approval under new section 505(j), generic applications for duplicates of drugs submitted under Section 505(b), new drugs.

I will not delve further into the particulars of the FD&C Act. But if you're very inclined, you can check the regulations yourselves.

I will say, however, that the new opportunity for abbreviated pathway for approval of generic drugs benefitted both the brand name industry, as well as the generic industry and its consumers, by offering new levels of exclusivity, and extension of patents, and then accessibility to new lower-priced generic products.

Again, I will not go into the intricacies of the legal aspects of those

amendments but will that developing the ANDA pathway was the key to quickly develop market safe and effective generic drugs.

So what do we mean by abbreviated? You need to consider what we expect in a new drug application and what we also consider to be essential in an ANDA.

So here's the list of the contents of an abbreviated new drug application, including the identification of a single Reference Listed Drug, RLD, the same conditions of use, active ingredients, routes of administration, dosage pharma strength, labeling, bio-equivalence, and safety assessment of the inactive ingredients.

I will highlight some of these momentarily, but I want to point out the word bio-equivalence as it becomes a very important concept later on in my talk.

This next slide continues a list of the contents of ANDA. And although I keep alluding to the term abbreviated, it still contains a lot of information that is required to

come to a regular determination of approving a generic drug or not.

Another term you'll see here bolded, which you'll hear me repeat during this talk, is pharmaceutical equivalence. This, pharmaceutical equivalence, or PE as we like to call it, is the chemistry manufacturing and control's basis for determining the sameness of the generic drug to the RLD.

And it comes as more than just a product itself, an extensive component to manufacturing, batch, facilities inspections, testing, packaging, stability.

You should also be aware, during this quick overview, that ANDAs are held to the same high standards for current good manufacturing processes. In a nutshell, these standards assure the quality of marketed drug products, both new drug and generic, and include use of compliance and surveillance inspections. This multi-disciplinary approach to development of generic drugs allows for consistency and quality for

those products that are on the market.

On this slide, you'll see a framework for generic drug development. It starts at the bottom. And each step up the pyramid relies on the level below it.

FDA starts its consideration of generic drugs by examining the basic chemistry of the active and inactive ingredients and then all the appropriate testing and manufacturing issues going to the assessment of pharmaceutical equivalence which is more focused on formulation. Only if the chemistry and formulation of the generic product are settled will FDA consider the next steps of bio-equivalence and then clinical relevance.

So I know I said a lot in a short bit of time, so we're going to go through these one at a time. So first, when I speak of an active ingredient or ingredients, I'm talking about the component or components of a drug that has the direct effects, as seen here, on diagnosis, cure, mitigation, treatment, or prevention of disease.

That's a complicated aspect but is really the focus on when we talk about the active ingredients of a generic versus a brand drug.

But the idea of sameness is not simply pulling a chemical off the shelf. You know, with generic drugs having patent protections and exclusivity, I mean, sorry, new drugs having patent protections and exclusivity, the generic manufacturer has to work around some of these to not obviate patent protections.

So generic products can be of a different polymorphic form or ester, and sometimes they have to use new analytical technologies to evaluate particle size to make sure that the generic is equivalent to the reference listed drug.

So the idea of pharmaceutical equivalence is set down in what's called the Orange Book or for approved drug products and is given here on this slide.

And I'm not going to just read this slide to you. But it takes you from the basic

chemistry off the shelf into what is considered the essential, basically, ingredients of the generic drug that have to be right and set to certain standards of strength, quality, purity, and identity.

However, even though the definition for pharmaceutical equivalence allows for differences between generic drugs and their brand names, there can be differences that are allowed, such as shape, scoring, release mechanisms, packaging, excipients, expiration time and, within certain limits, labeling.

I want to point out that there's a term, excipients, or an inactive ingredient that gets confused at times. And excipients can be added to drugs via fillers, extenders, et cetera, that are not specifically intended to exert a therapeutic effect. They are considered inactive ingredients but could aid in delivery by enhancing absorption or release.

An example of this would be like and extended release tablet that, if the patent on

the brand drug is a certain type of capsule with tiny micro-holes or something, and the generic has to give the same exposure, it may have to be in a wax type tablet or a different --- work around the patent protections to make sure that it acts the same in the body.

So we allow differences between a brand and a generic, but we hope those allowable differences don't have a different therapeutic effect or ineffect.

So we talked kind of about the chemistry in pharmaceutical equivalence. And now we have to add into it the clinical component or human component into generic drug development. That's why I pointed out bio-equivalence earlier.

Bio-equivalence studies are expected to demonstrate that both the generic drug and the brand drug will deliver the same amount of the active drug and active metabolites into to the bloodstream at the same rate for distribution to the drug's pharmacologic site of action.

These studies establish reliable

differences in the generic drug will not affect performance of the generic when compared to the brand in the body.

So typically, healthy volunteers are given a single dose of the brand or generic, blood tests are taken, and they're switched over the other product, and then blood tests are drawn again, and then pharmacokinetic analyses are performed. These are almost always exclusively done in adults and not children.

Bio-equivalence analysis includes a robust comparison of pharmacokinetic data for both the generic and the brand, including maximum concentration in area under the curve.

These measurements are surrogates for rate and extent of absorption of the product. However, to demonstrate bio-equivalence, the statistical analysis must show the ratios of generic to the brand of these parameters must remain within a 90 percent confidence interval of 0.8 to 1.25.

If that gets a little bit beyond your

statistical comfort, I'll show you a graph on the next slide to try to illustrate this concept.

Here you see two sets of curves. The blue or bluish-purple curve is the time to maximum concentration and overall area under the curve for the test or generic drug. The green curve is the data from the brand, or rather the reference drug.

On the left graph the curves for the test and the RLD are similar and overlie each other. So FDA would consider that. Based on this comparative pharmacokinetic data from bio-equivalence studies, the generic would be bio-equivalence to the RLD or brand.

On the right graph, both curves do not look similar in that the generic drug peaks earlier and has a smaller area under the curve compared to the RLD. So the generic drug, in this case, would not be considered bio-equivalent to the brand.

So why is bio-equivalent such an important concept? If we compare the application

requirements again between brand-named new drugs to generics, we see the chemistry manufacturing controls, the first five here are similar.

In order for ANDAs to be abbreviated, however, there's no need to repeat formal animal toxicity studies, bio-availability studies, or formal Phase 1, 2, and 3 double-blinded randomized placebo controlled trials in patients.

Why is that? This is because the active pharmaceutical ingredient has already been tested incrementally this way in both the IND and NDA phases for the new drug. So there's no need to repeat these studies for generic drugs.

So in essence, FDA allows the bio-equivalence analyses to stand in for those animal, clinical, and bio-availability studies. This is the basis for generic drug approvals in humans testing.

So we've reached towards the top of our pyramid now which I showed you a few slides ago. And now we have to consider the clinical relevance. That's to say the active ingredient

must not only be delivered, but it also must do so in the same clinically relevant way, as does the brand in the target population.

So an example for this would be if I had a patch that was for, let's say, blood pressure. And I had the brand, and it was applied to the skin, it would have to deliver the drug appropriately. And if I had a generic patch, then that generic would be expected to also deliver the drug in the same clinically relevant way.

If that generic drug fell off the patient, or got destroyed, or wasn't adhering well, and it didn't deliver the product well, it would be considered what we have on this slide, therapeutic inequivalent.

Because that's the idea. Is the product being associated in the same clinically relevant way? And these are concepts that are coming quickly, but these are all of the issues that we consider when we begin to consider the safety aspects of generic drugs.

So again, why worry about generic drug safety if we have a pharmaceutical equivalent, bio-equivalent, and therapeutic equivalent product? Shouldn't all generic drugs be safe and equivalent if the brand's been tested through animal studies and human clinical trials?

Well, the thing is that there are unexpected safety considerations and concerns that occur before and after marketing a generic drug. That's because, when the generic drug goes on the market, a larger more diverse patient population starts to use it that couldn't get access to it when it was a brand.

Also, a lot of generic drugs, since they are more easily available, get used off-label. So the safety issues may arise as the population changes.

In order to address these kind of issues, we try to look at the safety of generic drugs both before and during end of review, and then post-marketing.

So luckily, there is a regulation that

became a final rule in September of 2010 that spelled out that FDA wanted to see expedited safety reports for the bio-equivalent studies. This is also in guidance. However, this only applies to US studies so that the remaining adverse events that occur in bio-equivalent studies globally are only seen when the ANDA comes in to be reviewed.

We have two medical officers who look at these expedited safety reports, like Dr. Kortepeter was talking about the 15-day reports, they'll come in from the bio-equivalent studies.

This is our only way to know if something's going on in a bio-equivalent study before the application comes in so we can get some clue if there's a problem with either the patient population or the formulation of the generic drug itself. This helps us look at emerging safety issues of concern.

Then we take some of our information, and then when the ANDA comes in and is reviewed, we can help give our insights for the bio-

equivalence and clinical reviewers.

More commonly, however, we focus ourselves on generic drug safety once generic drugs are approved and marketed. Post-marketing surveillance of generic drugs provides assurance that other unanticipated factors of variability that would result in therapeutic inequivalence would be identified early. These go back to some of the quality problems and suspected product inferiority in our previous example.

I want to quickly note that the scope of generic surveillance is not focused on the active pharmaceutical ingredient. That's the work of CDER's Office of Surveillance and Epidemiology. What our group does is complimentary to those of OSE.

Therapeutic inequivalence can be the reason for complaints when patients are switched from a brand name to generic or from one generic to another generic.

These different generics may have problems with quality or other concerns related

to these new unanticipated safety concerns that may arise from allowable differences in the generic and the broader population that's being exposed.

These could also relate to off-label use. Sometimes they even feel this complaint is about the packaging or the device, such as a different dropper, cap, syringe, or injector.

I think there was a long list of quality issues and complaints that our group has seen that have led to concerns of therapeutic inequivalence of generic drug products.

The picture on the slide relates to a health hazard evaluation sent to our staff for review earlier this year. The lots these pills came from contained several larger than normal tablets. This came from a defect in production.

The clinical safety surveillance staff clinical reviewers had to consider the safety concerns related to these larger tablets such as, for example, how would they split or crush? We felt that these non-uniform tablets should be

removed from the market due to potential safety concerns.

So where do we get post-marketing safety signals related to generic drugs? Well, as Dr. Kortepeter noted, we get these from the public directly through MedWatch reports submitted to the FDA. Sometimes we'll get things emailed directly to our office director, Dr. Uhl.

We can detect problem products in our internal databases or through sponsor reports, sometimes in the literature, and sometimes from surveillance colleagues in other offices, and even in other agencies. However, Office of Generic Drug's definition of a potential signal might be different from that of the Office of Surveillance and Epidemiology.

We primarily use an internal database at FDA called the Drug Quality Reporting System. This is a subset of MedWatch reports that mostly contain complaints related to quality or inequivalence of drugs. These drug quality reports may also contain adverse event

information and therefore be the same reports that are in FAERS.

The Clinical Safety Surveillance staff reviews approximately 600 DQRS reports per month, and we focus on problematic generic drugs that we think we should evaluate further.

This is just a picture of our 101B DQRS report that is in the internal database just to kind of show you what we're dealing with. But luckily I have some good staff who can take the data from this system and export it into Excel spreadsheets for sorting and analysis.

We have a custom SAS program written by our staff that is used to analyze the complaints to identify new potential safety signals. If we think we have a problem with a new safety signal, we'll go back to the individual narratives in the detail of the reports, the MedWatch reports, to identify any single reports that we may require further review.

Sometimes, this slide is old, but

instead of IMS what I should say is IQVIA now. I guess we wrote this back in March. There's a source that distribution marketing did that the Office of Surveillance and Epidemiology uses. The short name is IQVIA. And it's about how drugs are distributed and marketed. And this is just data the comes in that we try to use sort of to look at the market share of multiple generic manufacturers.

Over many months, generic manufacturers will change. So the drugs that patients get month to month may be different manufacturers. And that also can lead to a problem with a patient feeling that maybe this month my drug didn't work and the previous one did.

So trying to look at what drugs were on the market at the time of complaints might sometimes help us to identify a particular manufacturer of a product. So we try to use the drug distribution data to create a true relative rate.

For example, if we got a complaint about a product from a manufacturer that had only about five percent market share, but we received a lot of complaints, we might think that's more important than five complaints from a manufacturer that had 80 percent of the market.

So because it's been very difficult to figure out where to put our resources, we're trying to use drug distribution data in different ways to help our staff decide what signals to focus on.

So there are two basic ways to consider the ongoing stream of safety data related to generic drugs and generic drug quality. We can look at them both retrospectively and prospectively.

With the retrospective look, the safety evaluator reviews a single month of these DQRS complaints to identify any single report warranting scrutiny. Those reports are sorted by manufacturer and product to identify clusters. For a single manufacturer, again, that might

indicate an emerging problem. These signals are discussed at our monthly committee meeting which I'll talk about next.

Another thing that we try to focus on in our group is to focus on the new generics that are being approved and put them on what we call the newly approved generic watch list. This is especially important for first generics in a class of products.

During each surveillance period, the safety evaluator in our group will review the new generics watch list and search for complaints related to these products. Some of these are expected, and it's called the Weber Effect.

But sometimes we find that when a person goes from brand that the first generic or two that gets on the market, because the uptake is sometimes very quick because the price drops after they get on the market, that we sometimes get a flood of complaints all at once.

And we have to sometimes wait on that for three, maybe six months until we see if that

particular quick signal of, you know, uptake goes away. If these new generics meet a certain signal criteria we've created, then we continue to monitor them.

Sometimes when a potential signal is confirmed, then we have to do a more in-depth analysis. And this is where we look back at the safety, quality, or therapeutic inequivalence for a signal. This might include going back to the application, the ANDA, or the information in the brand drug.

This can involve conversations with our Office of Pharmaceutical Quality staff regarding recent chemistry and manufacturing changes along with asking our colleagues across FDA's field offices.

The safety reviewer might review bio-equivalence data, market share data, or other scientific or medical literature to look for clues as to why this particular generic product might be a problem.

In fact, the safety reviewer has to

consider any and all of what we call critical elements that are involved in the development of generic drugs, which again helps me review what I said in the beginning of my talk, about how chemistry and product-related elements in pharmaceutical equivalence, then through bio-equivalence and clinical intent of product design leads to therapeutic equivalence.

The slide is a little busy, but it just basically reminds us that we have to consider all things, including inspectional issues, labeling, and other legal and regulatory aspects that may enhance or limit our ability to take action on a safety concern.

I don't just want to end this talk by having you understand that generic safety surveillance is a collaborative effort across CEDR's super offices. Once the individual safety evaluator team has evaluated the issue, this issue is first discussed at our monthly clinical safety surveillance staff's Safety and Surveillance Committee meeting.

The monthly meeting coordinates between the sub-offices in both the Office of Generic Drugs and the Office of Pharmaceutical Quality. The decision of whether to open a drug safety issue in our internal database is considered as well.

The monthly committee, if it can't make a decision, then brings its safety concerns to the larger bi-monthly OGD Safety and Surveillance Committee meeting which has representation from all of CEDR's super offices. The bi-monthly committee helps to make a final decision on the controversial or emerging issues.

And that gives you all some insight into the generic drug development and safety evaluation. I want to acknowledge those individuals who provided slides and guidance for my presentation. I thank you for your attention.

CHAIR DRACKER: Thank you, Dr. Chazin. We will - I just want to mention that the public hearing period is now closed. It closed at 10:16. We will now proceed with questions to the

committee and panel discussions.

I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except for the specific request of the panel.

So in summary, the pediatric safety review for Escitalopram focused pediatric safety review is concluded. No new safety signals were identified. The FDA recommends to continue ongoing postmarketing safety monitoring. Does the pediatric advisory committee concur? Go ahead.

MEMBER SAYEJ: Thank you, Dr. Dracker. This is Dr. Wael Sayej from Connecticut. I just have a couple of questions, one with regards to the drug ineffectiveness reports. Do we have any idea if there's any reporting of the length of time that these patients were on the drug before it was deemed or before it was labeled as ineffective for them?

The second question I have is did any of these patients have pharmacogenomics done

before starting an SSRI which is, now is the current trend in treating patients with SSRIs by performing pharmacogenomics to look at their metabolic pathways to figure out which SSRI is most effective for them?

CDR SUGGS: I can take that. So in regards to your first question, do we know the length of time, no, we don't. We only know what is reported, and I believe in these five cases that it just stated there was a switch, but we don't often have that information as in, "I started on this date. I switched on this date," and so forth, so we don't. We don't have that in short in most of these cases.

Secondly, no, these cases did not report pharmacogenomics. Again, we're limited by what is reported to us and it was not reported in these cases.

CHAIR DRACKER: Sarah?

MEMBER HOEHN: Sarah Hoehn, I have two more questions for Dr. Suggs and they are related. On your slides when you talked about

the number of prescriptions, you had it broken down by under 16 years of age, but I didn't know if you had any data based on those under 12 years of age?

And that's related to my second question which was when you looked at the safety data, you excluded suicide since it's already a known risk, but I wanted some clarity around that because it seems as though it could be new information if there's a higher suicide rate in the seven to 11-year-olds, so those were my two questions.

CDR SUGGS: Okay, so I'm trying to look back in my slides. I don't believe we had any for the breakdown on the age group. I think we just had in this case the zero to 16 and did not further break it down for this particular review. And for your second question regarding suicide and increased severity, it's already a boxed warning, so I don't know how we could elevate that further. We already have it labeled at the highest level we

could label it, so I don't know how we would take that any higher.

MEMBER HOEHN: I just didn't know if there seems to be a higher rate in the seven to 11-year-olds, if something could be added about it being contraindicated or other markers because clearly the rates of suicide in a seven-year-old are much lower than the rates of suicide in a 15-year-old.

So to me, there is actually a difference because a seven-year-old committing suicide should be a never event and we can't prevent every teenager, so to me it actually does make a difference based on age.

DR. LEVIN: Hi, this is Bob Levin from the Division of Pharmacovigilance. I work on the team with Dr. Suggs on review. That's something we could look at. We could actually look at the data to see the age breakdown and whether there are completed suicides versus other less severe events or other severe events, so we could look at that.

The question, and depending on what we found, the question of rates is very difficult with FAERS. It's really virtually impossible to really get true rates, but it's a good point whether there may be a signal in a - it would be hard to try to figure out, but we could take a look at that looking at our data.

MEMBER HOEHN: But you could filter the FAERS by age, yes? I mean, there should be some way to get the data if there were any completed suicides in the seven to nine-year-olds.

DR. LEVIN: Yes, we could look at that, and maybe we could do it before this afternoon or at some point, but we could take a look. My recollection - I mean, the completed suicides are so extremely rare. I would - I'm not even sure - well, we'll try to find that for you if we have a chance and it's something we could potentially look at theoretically.

It depends on how many events there are and what type of information, and even though

we can't calculate rates, we understand your point that if you looked, if you saw a signal or a potential signal, it would be concerning, so we can try to get back to you.

CHAIR DRACKER: Dr. McCune?

DR. McCUNE: Just a reminder that the drug is only labeled for 12 and above, so we can certainly look as we've been talking about, but the label is for 12 and above.

MEMBER HOEHN: That actually relates to my first question though which was about even though it's labeled for 12 and above, if we have any data on the seven to 11-year-olds that are taking it even though they're taking it off-label. I think if there were, you know, a rash of completed suicides around eight-year-olds, it would change peoples' practice of the off-label use.

CHAIR DRACKER: David had a question, but Jim has one comment related to this discussion.

MEMBER McGOUGH: I could just - Jim

McGough, child psychiatry. I can just, I can comment on a couple of points. First of all, these data are from community use. They're not from clinical trials, correct?

CDR SUGGS: The drug use data?

MEMBER McGOUGH: Like the suicide that was reported. It's clinical. It's community - the problem with this is that pediatric depression is really, really messy and there are certainly some individuals who truly have biological depression going on and they respond to the medicine. The problem is a lot of these kids have horrible psychosocial situations. They've been abused or they're neglected.

There's huge noise in the system and I was part of the group that put the black label on it, which was probably a mistake, but the community practitioners just, they hear depression and they give this, not always with full assessment.

So sometimes out of these chaotic bubbles, kids try to hurt themselves or talk

about hurting themselves, and I'm not even sure if this was a completed suicide or a suicide threat, which there's a difference there.

In the studies now, you know, they differentiate suicidality which is, you know, any thinking about it, etcetera, with the Columbia rating, and most of it is just kind of some vague threat.

So I think a single incident or even a very small incident probably overstates the risk. Practitioners take the burden, and I think honestly, a lot of doctors overprescribe these drugs, especially in these younger kids, but that's kind of their call.

In terms of, you know, the other issues you were raising, it can take three months to get a response to these medicines. The testing, the genetic testing is mostly to just see if they're slow metabolizers of the drug.

It really has - the commercial companies selling those tests want to make more to do at this point. There's no consensus that

that's even important in spite of its commercial appeal. So, you know, my sense is that there isn't really any new news here.

Doctors do use off--label drugs and I think the burden then is on them to at least be aware of this, but with this population, these risks of self-harm are just endemic to it, and without controlled trials, we really can't make a judgment about the drug effects. I think the warning now is, if anything, is more than we need.

CHAIR DRACKER: Did you want to comment?

MR. META: Hi, yeah, sorry, my name is Shek Meta. I'm from the Drug Utilization Service in the Division of Epidemiology. We - with respect to the question -

CHAIR DRACKER: Speak into the microphone, please.

MR. META: Sorry, yeah. With respect to the question about the number of patients, these are a nationally estimated number of unique

patients based on a proprietary algorithm that our data vendor uses, and so we are able -

We don't have the age stratification right now, but moving forward, we may be able to get it, the age stratification that includes seven to, or, I'm sorry, 11 through 16-year-olds.

CHAIR DRACKER: Okay, thank you. David, you had a question?

MEMBER CALLAHAN: David Callahan, child neurology. You had a slide that showed seven of nine discontinuations from psychiatric adverse events and another figure on the slide was 29 percent neurologic adverse events. What were those psychiatric and neurologic adverse events?

CDR SUGGS: I don't have those on hand. I don't know if there's the division here that could answer that. I don't have those on hand for me and I don't know if there's somebody here that could answer it.

DR. LEVIN: Oh, is this about the discontinuations in the study?

CDR SUGGS: Yes.

DR. LEVIN: Yeah, we have those. As I'm looking for those, the one I recall that was likely or possibly or probably related to the drug was an episode of mania in one patient. There were no deaths in the study. Let me find it for you, sorry.

But they were fairly common background events in this population, which while some of them were possibly related to the drug, there was no strong indication and the investigators did not think any of the other events were related, but I'll give you the details as soon as I can.

Yes, okay, so one event was mania. One was suicidal ideation without behavior. One was agitation, daydreaming. These are all each single cases, daydreaming, dissociation, impulsive behavior, and insomnia, and two of those that were discontinuations also were categorized as serious adverse events which were mania and suicidal ideation.

CHAIR DRACKER: Any other questions or

comments?

MEMBER OSTER: I'm Randi Oster. I want to take a moment to first talk about the data collection and then I'd like to address some of the labeling issues from the data that we have.

The first thing I'd like to say is that I am happy to hear that it is included in the postmarketing adverse drug experience that if the drug doesn't meet your expectation, what they call expected pharmaceutical action, you count that because that's important.

And the reason that's important, I go back to my aerospace where we looked as a defect as something that doesn't meet expectations, and so therefore, that definition is valid because that is what the patient is looking for.

So then when we look at the number of results that have been reported, we see over almost four million, and then we looked at 247,000 were coded as drug ineffective, and then there were 43 events that you actually looked at,

and the point here is there's a lot of information and we have limited data.

And so my question to the group that I don't expect you to answer, but I want you to understand from my point of view, is in aerospace when I was putting new products on jet engines, was lack of information a reason for us to say, "Put it on the plane"?

And therefore, as we then look at the labeling and the information we have to make this data, we see, and we've talked about the 74 deaths, we see labeled events at 55 and we're not counting them because they're already labeled.

Fifty-five is statistically significant when we're looking at how many we're actually counting. Why are we still having these problems and why aren't we addressing them? And therefore, for me on the label, I have a couple of suggestions.

The first is when we talk about adolescents, we don't define the age there, and I think it is important that people - sometimes

people call them tweens, right? You know, why aren't we saying, "From zero to 12, this is a no"? It's not here.

I also, as I read the information, there's no talk of alcohol and does alcohol affect this drug? Is there any correlation? I don't know because it was not discussed.

The other one, it is not clear on the labeling that we don't know the long-term effects of this drug, so the studies are done for up to 24 weeks, but how long are these children taking the drugs? And so therefore, as we look at these drugs, I think in the, with the data we have, we have to make a decision to see does this help families choose a course of action?

CHAIR DRACKER: Are there any comments?

DR. ALEXANDER: So I will try and address at least some of the comments that you're making with regards to what we look at.

I do think that for psychiatric drugs for chronic use first of all, that we do have

trials that try to look out to six months and then usually get at least some continued experience on those patients sort of who felt like the drug worked for them to continue to use the drug in ongoing safety trials so that we get data out to a year.

We recognize that we have a limitation of not really having the ability to look at a drug over a period of years of use within the adolescent studies in order to try and address, you know, are there other considerations? We know that's a limitation, but we still have to deal with what we can feasibly get within the setting of a clinical trial.

That's part of the reason we do these kind of postmarketing reviews afterwards to see if there are other concerns that are gathered not only with the use of the drug acutely, but the idea that is there something that we can identify as an adverse reaction or something that's going on that is recognized as an adverse effect of the drug.

And we are looking in other ways to try and get some additional information on drugs when we do know that there is an adverse effect. Some of the drugs that we're talking about in the psychiatry realm have effects, say, on weight gain and growth, and we are doing other studies to try and take a look at sort of those effects separately.

So in terms of your comments with regards to the additional data that may be there within the adverse event reporting system, I would see if any of the other individuals from either OSE or the Office of Generic Drugs do have comments related to those.

But the study that was reported by Dr. Kortepeter was really sort of trying to do what we could to take a look at how we could describe for people on the outside what we have received and what we are doing in order to sort of try and take a look at those reports as well as the presentation from the Office of Generic Drugs from Dr. Chazin about what they actually do to

take a look at these.

I will say from my own experience, we've, I've been involved previously in reports where we've looked at issues that have come up because of drug quality and it happens not only for the generics, it happens for the brand-name drugs as well, which was the area that I used to work in where some of these reports have led to issues where we've had to recognize that we've had to recall certain lots of drugs or things like that because of these kinds of experience.

But the issue of trying to sort out the meaning of a report that comes to us about a drug being ineffective is really difficult when you think about it within the setting of the clinical trials. We have all sorts of patients that are reporting that the drug is ineffective. It's not like the drug is expected to be effective in everybody in whom it's used.

CHAIR DRACKER: Was there any information regarding concomitant drug use or alcohol exposure as she mentioned?

DR. LEVIN: During the study or in clinical practice? Could you please repeat your question about the alcohol? Are you asking in general is there a pharmacologic effect, interaction with alcohol?

MEMBER OSTER: Yes.

DR. LEVIN: Not that we know of. There's a brief mention on the label suggesting there's not an effect. So we don't have direct information, but in general though with SSRIs, as far as safety, they're more similar than different, and I can't recall any SSRI that has a documented true drug interaction effect.

But another way to look at it, I think perhaps another point you're making that concomitant use of CNS depressants can pose increased risk, so, and I think the labels are somewhat, they're probably not completely consistent.

Some of the labels probably do suggest that you have a general warning for CNS depressant effects and suggest caution in

considering using concomitant use of CNS depressants and alcohol.

Lexapro is not thought to be a CNS depressant, but there are obviously certain neuropsychiatric effects, but it's a good general point that - I think part of your point is concomitant use and additive risks -

MEMBER OSTER: Yes.

DR. LEVIN: - as well as whether or not there's a direct pharmacokinetic effect, which there's not with alcohol.

CHAIR DRACKER: Dr. Havens had a question and then Dr. McCune.

MEMBER HAVENS: Thanks, I just wanted to clarify that it's possible to collect the data on usage and adverse events under age 12 and between ages 12 and 18, and then -

Yes, it is because there are, when you look at the 12 adverse events in the, whatever it was, 0 to 16 age group, three out of those were in the six to 12, and if that's really a very small number of people using the drug, then the

prevalence of these adverse events that are addressed here might be much higher.

So understanding the denominator becomes a useful part of and would potentially lead you to identify a signal for a higher rate of adverse events in the - so you could say something other than, "Safety and efficacy have not been shown." You could say, "Epidemiologic evidence might suggest that safety is not good under age 12."

Likewise, if the - I understand and I appreciated the discussion about the, "This drug doesn't work," problem, but if many of those reports are coming in that younger age group, then it would be interesting again to be able to get to what was stated in the open public session that the efficacy in this age group may - you might be able to - well, I don't know. That would be the question. Could you ever, can you ever get to enough data that you believe in to be able to say something like that?

DR. LEVIN: Postmarketing data

specifically?

MEMBER HAVENS: Yeah, like, "Don't use it under age 12 because it doesn't work."

DR. LEVIN: Yeah, let me make a few - I'll try to address that then step back a little bit. I mean, overall for our review, for our pediatric review, as a large majority of our review, we really did find - we didn't find any new unexpected adverse events. That's probably the most important -

MEMBER HAVENS: Yeah, no -

DR. LEVIN: - point of all.

MEMBER HAVENS: I got it. I got it. I'm with you, yeah.

DR. LEVIN: But, yes, it's always, of course it's always ideal to have a denominator. We almost, we never do in postmarketing. We just never have a true denominator, but usage data can of course give you suggestions.

The other major point about the postmarketing data is such a high proportion, as with many psychiatric conditions both in adults

and pediatric patients, the great majority of adverse events tend to be reflective of the illness and very likely related to the illness under treatment. That's what we actually found.

So I think part of your point, the more of course we find an unusual, unexpected adverse event that might have some pharmacologic connection, that of course would lead us to a much more detailed analysis of potentially trying to get more denominator data and trying to find the rates, but I agree with your points.

Those are all ideal to have and we, without any systematic study, we really can't calculate rates. We mostly do a qualitative review. When we're doing postmarketing review, our number one goal is to see qualitatively what types of adverse events do we see, and the more we find something new or unexpected, the more we would pursue a more in-depth evaluation that you're suggesting.

MEMBER HAVENS: Right, but can you break up the usage date -

DR. LEVIN: Yes.

MEMBER HAVENS: - into those age groups?

DR. LEVIN: Yes, we can.

MEMBER HAVENS: So that would allow you some way to - I understand that it's an imperfect world, but -

PARTICIPANT: No, you're right. We could do that. I mean, in this case, there's no need to do that so far from what we've seen. Given that we don't find any new concerning adverse events, it really is the most important point to decide whether to do anything further.

But for the splitting question like you asked, your colleague asked about were there completed suicides, we can give you answers to that and then take the next step, but I'm sure not if that addresses the point you're making. Is that - it's very hard. We can always try -

MEMBER HAVENS: No, I understand.

DR. LEVIN: It's one of the last things. We actually can almost never - I'd say

it's probably safe to say we can never calculate rates with postmarketing data.

MEMBER HAVENS: No, I agree. It's a huge challenge, but part of the issue here is using drugs off--label, and if the best we can say is, "Well, don't use it off--label," well, then, okay, but if you can say more like, "You know, off--label use really is looking ugly," then that's potentially useful if you could ever do that.

DR. LEVIN: No, I agree. I can't think of examples now thinking of other drug classes. There's, you know, a small number of cases where that scenario has played out. I can't really think of one right now, but I'm sure if there are specific adverse events with specific findings, you might come to that conclusion for certain drugs.

CHAIR DRACKER: Susan?

DR. McCUNE: So I would just say that we have had this come up in the past in terms of questions from the committee where we might be

able to take them offline to be able to look at them.

I think what we're looking at right now is, so we're looking at FAERS reports and we're looking at some use data. I think in order to answer the question that you're asking about off-label use and adverse events associated with off-label use in that population is really one that we would need to do a study.

We would need to look at some of the databases that we have independent of what, databases that are available, not that FDA has, but databases that are available where we could work to answer this question in terms of off-label use and potential adverse events, and if that's something that's of interest to the committee, it's certainly something that we can take offline and then report back to the committee on.

MEMBER HAVENS: The label notes that the AUC is smaller, the peak is higher, and the time to peak is shorter in the adolescents. And

you wonder if there's not a continuing change in absorption, and distribution, and metabolism in the younger group that might actually lead to a biological reason or a kinetics reason for a difference in side effects.

DR. LEVIN: Yeah, that's, what you mentioned is correct about the PK differences. On the other hand, for this, this drug is actually an immediate release formulation, and maybe more importantly, the half-life is extremely long, you know, 27 to 38 some hours.

So in that case, it probably would be much less of a concern than if it was a shorter half-life drug. That's one factor, but - I'm sorry, go ahead.

Yeah, the other important thing about antidepressants and their mechanism of action, while we can't claim in most cases we know exactly the mechanism of action, there is a lot known about the mechanism, and typically these drugs, as we've mentioned already I think today, that antidepressants have a very long latency of

both onset of efficacy and full efficacy.

Typically you don't see anything in trials for the very least one week to two weeks. In the clinical practice, it's very common for a full effect to require four to eight weeks and sometimes more.

So the PK, that's absolutely true. The points you mentioned are the PK profile, but knowing how the mechanism of PD action is, it will hard to think of a, something to point to a direct concern tying the PK and PD together for this drug.

MEMBER HAVENS: Thank you.

CHAIR DRACKER: Dr. Turer?

MEMBER TURER: So those were excellent points that you brought up about the PK and PD data, and I echo that. For younger kids, if we were to actually look at efficacy, I think that that would be important.

But the other thing is because the half-life is shorter and we know that children are very hesitant to take drugs, the question

about efficacy in the setting of spotty adherence is a concern in postmarketing data.

The other concern that I have is in pediatrics as opposed to internal medicine is we frequently compound these drugs, and so for younger children, are they getting compounded? And when we're talking about generics, do we know about bioequivalence in the setting of compounded drugs and how they're administered once they get into the home? Are the parents shaking them up?

The other thing I frequently get asked by parents is, "May I put this in the milk?" right, or, "May I put it in a drink?" So once you suspend a drug in another compound, what is the impact on the biologic properties of the drug? And I think that for children, that's incredibly important.

So to think about the bioequivalence not just in terms of the tablet and the compound within that tablet, but the actual use that's happening in the community and the adherence, we just can't factor that in in these postmarketing

data.

DR. LEVIN: Well, I think the first point maybe about the half-life, actually Lexapro has a very long half-life, so it would tend to mitigate against some concerns about differences among patients or with the teen groups, so that was the -

MEMBER TURER: But shorter than, say, Fluoxetine or Prozac?

DR. LEVIN: Oh, yeah, well, that's the longest half-life drug, yes, about four to six weeks of the active metabolite, but still 24 to 32 is a very long half-life compared to most products, so I think that alone, for that point, we wouldn't necessarily have concern about PK effects or PK/PD.

On the point about it compounding, are you referring to not just concomitant use, but actually changing the formulation or actually crushing it, we'll say putting it in an NG tube or things like that? Is that what you're -

MEMBER TURER: Correct.

PARTICIPANT: - referring to?

MEMBER TURER: Right, I mean, we have many, many preadolescent kids who just refuse to take pills. I mean, these pills are fairly small. I mean, I have my patients bring their pills all the time. They're tiny, but nevertheless, it can be a real challenge.

DR. ALEXANDER: Understood, but I would point out that actually Lexapro is available as both a tablet and an oral solution, so there is a formulation that could be used in the younger age ranges.

I would comment on the previous discussion too with regards to what's known about the fact that the exposure looks somewhat different in younger children.

One, again, that comment may have been made in the labeling, but it points out that we, for the adolescents where that length of exposure was lower, we still had clinical trials that showed that the drug was effective despite the fact that the profile looked somewhat different.

And even for the trials that would have been conducted in younger kids, I think they would have taken into account what they were expecting in terms of the overall exposure to the drug when they decided on what dosing that they would have used to study in the clinical trials.

Despite that, we labeled the drug saying that we didn't see any issues in the safety study. We didn't see any issues with regards to safety in the younger age population, but the drug was not shown to be effective in that population and that's why it's only labeled for 12 to 17-year-olds.

MEMBER TURER: Right, and I guess my point is when you do the bioequivalence testing, are you testing both formulations? Are you testing the liquid separately?

DR. ALEXANDER: So I would say typically when we are looking at labeling for a new drug, if they're coming in with a different formulation, we are typically also evaluating the bioequivalence of those things.

The bioequivalence of the, whether an oral solution is bioequivalent to a tablet, we would usually expect that, but we do have examples of the opposite where the bioequivalence wasn't demonstrated and then they had to actually show the separate effectiveness of the dosing, and it's usually reflected in labeling whether the dosing of the oral solution is the same or has to be limited to a specific population in whom they showed the effectiveness of it.

So most often what we see is that the oral solution is considered bioequivalent to the tablet, and in those instances, we basically have the labeling reflect that the dosing could be either one or the other.

In the specific instances where the product isn't considered bioequivalent, then we would usually give instructions of where you use the solution or where the solution was proven to be effective and the fact that these things aren't considered interchangeable.

DR. CHAN: Hi, I'm Vicky Chan.

MEMBER PORTMAN: Can I comment on that?

CHAIR DRACKER: Dr. Portman, was that you?

MEMBER PORTMAN: Yes, it was.

CHAIR DRACKER: Did you have a question?

MEMBER PORTMAN: Yeah, I do. The question was just a follow up on the recent answer from FDA. Does the generic solution, has that played a role or been looked at in the effectiveness story?

DR. CHAZIN: Hi, this is Howard Chazin answering. Any generic has to follow on from the brand, so the bioequivalence measures against, compares to the brand first. So you couldn't have an independent generic with a different bioequivalence marketed.

So just to be clear, you're talking about two separate things. You're talking about different formulations of a new drug and then the follow up~~on~~ generic has to match the new drug to

be clear. Thank you.

CHAIR DRACKER: Go ahead.

MEMBER PORTMAN: Thank you.

DR. CHAN: Hi, this is Vicky Chan. I'm a team leader, one of the team leaders on the Division of Pharmacovigilance. I also worked on the Lexapro review.

I wanted to comment and clarify on a previous question regarding the lack of effect cases that were identified in this review. They were patients age 11 to 16, so there were two patients under 12, but I also want to caution, I wanted to make sure that we don't extrapolate efficacy from these cases because they're not really lack of effect cases.

They're actually product substitution issues and product quality issues that we're trying to address, so I wanted to make sure folks know that to be careful about extrapolating efficacy data from these cases. Thank you.

CHAIR DRACKER: Yes?

DR. HAUSMAN: Hi, Ethan Hausman.

There was a statement a little while ago and I want to caution the PAC. Suicide in six to 12 should be a never event in a generally unselected population.

I apologize, either NIH or CDC has an online calculator and you can parse down by reports of suicide by age group in different year categories. When I was doing safety reviews several years ago in OSE and then also in DPMH, you start getting drips and drabs sadly starting at about seven to eight years old.

In my own practice, we had a child swallow some garage chemicals and everybody reported it as accidental exposure until I said, "Did you do this on purpose? Were you trying to kill yourself?"

So it's sad and it does happen, and it should be zero, but it's not, and with the cases that were actually shown being confounded - I believe one case was oppositional defiant disorder and there may have been another diagnosis.

While I agree with everything the PAC is saying, and it's not my role to comment on the viewpoint on how anybody should vote, these are complicated cases and they're with off--label use in a not indicated age.

I think all of the questions that have been brought up are great and I think we should move forward with PAC suggestions, but I just wanted to voice my perspective that in these kids, unfortunately we do have a signal. The question is how to parse it out and how to deal with it moving forward.

CHAIR DRACKER: I think a comment that was made, and I don't need you to comment back again, but the issue that children don't medications the way they're intended necessary. They chew them. They cup them. They take them with other substances, so it changes the kinetics and it changes the absorption rate of these drugs as well.

It's something that I don't think we really discuss enough of and, I mean, I see

children in my own practice that take drugs that are specific to the enteric absorption rate. Once they're taken whole, then they're chewed, they're crunched, they're mixed with other things, anything parents can do to get them in, and we don't always consider that issue.

I think Dr. Wade had a question, then we'll go to Dr. Flick and then Dr. Jones, I believe. Did you have a question? Okay, that's fine, then you're first. Go right ahead.

MEMBER JONES: Thank you. I actually had a question regarding the bioequivalence for the generic products. So is bioequivalence testing done specifically in pediatric populations?

DR. CHAZIN: No, it's not. It's not. Really, that's not part of the original statute. It kind of predates pediatric statutes and that's probably why because Hatch-Waxman was intended to, you know, bring out, you know, bring this forward. So it's always done in adults.

There may be some really rare bio INDs

for specific drugs like pediatric cancer or things like that, but that's very rare. So almost always we're doing adult extrapolations from the brand and then the labeling follows on on the generic because once it's established in the adult bioequivalence, then it - again, the labeling is always led by the new drug.

MEMBER JONES: Yeah, so in the postmarketing evaluation, do you look at pediatric subpopulations to determine if there's a different, you know, signal there in the pediatric population?

DR. CHAZIN: That's a good question. I - we have not - well, you know what? I'll have to say a lot of this is stimulant products that we're having issues with that people say are ineffective are in pediatric populations, so that's a very common generic complaint. "These are not working." We have them mix amphetamine salts in adults that we have.

Every month, we see certain stimulants that are being complained about and returned to

the pharmacy, "This doesn't work." We're trying to get at that. Is it formulation? Is it a company? Is it particular lots? We're still working on that, so that's still out, but we do look at target populations when we're considering evaluating what's going on.

MEMBER JONES: Okay, thank you.

DR. LEVIN: Yeah, if I can follow up on Dr. Chazin's point, we worked very closely with Dr. Chazin's group on particular scenarios that maybe one, that you're referring to. The stimulants is the first thing that came to mind.

So one point with the stimulants, one thing that also helps guide us in trying to figure out how to triage and how to allocate resources and look into these lack of effect reports is really kind of a risk-based approach, meaning that typically for immediate release products, we have a lower level of suspicion there might be a problem. For modified release, that may shift our equation.

So probably to address several

questions in the room, those are factors we take into account when trying to figure out when to address whether or not there may be something, you know, something beyond just a signal or potential signal for lack of efficacy if it's a complex product like, let's say, a transdermal product, or a modified release, or a neurotherapeutic index drug.

Those are things that help us, both OSE or OGD, collaborate, have a more active, direct approach to following up on suspected lack of effect if there's other factors about the API or the product that would make you a bit more suspicious.

But in that, your question is more specific. Do we have - I mean, is this about pediatric focused lack of efficacy reports or just more general pediatric pharmacovigilance?

MEMBER JONES: Well, my question was more related to the bioequivalence, the fact that they're not done in pediatrics, and if you have, you know, potential signals, you know, like we

saw there were several reports of, "It's not effective."

Do you look to see is this different in what's being seen in adults, and if you do, does that lead you to consider further bioequivalence studies or other types of studies to determine whether maybe this drug is acting differently in kids?

DR. LEVIN: Yeah, I guess my main answer is that more than comparing adult and pediatric bioequivalence data, we probably focus more on the nature of this particular product and we might look into the actual product quality.

More than comparing previous preexisting premarketing data, OGD, and OSE, and OND would hone in on the particular facts of that product if that makes sense. It would be - and that would be considering, I think, previous adult data too, but that probably doesn't answer your question directly.

MEMBER JONES: So you're saying you would look at the specific molecule and determine

are there pharmacologic properties where children may metabolize the drug differently or - is that kind of what you're saying that you do?

DR. LEVIN: Yeah, that's one issue, and the other issue is a lot of it's formulation or level of risk, whether it's modified release or a complex formulation.

But I guess maybe one way to answer, what I was trying to get at is that the more you have suspicion of a potential problem with a drug, and Dr. Chazin referred to this as well, we really do sort of a full range complex analysis that would involve looking at the actual postmarketing product, maybe getting samples of the product, doing physical testing.

I guess it's a complex answer of how to address these potential signals in more detail, but we are developing more of a systematic approach to decide when to pursue.

And again, to remind you of Dr. Kortepeter's point, in all of FAERS, all of our postmarketing adverse event reports for all

drugs, adults and pediatrics, the most common category of adverse events are lack of effect, so that makes it a really, really complex problem. When do you do further investigation?

There are so many factors to consider and that would be one. If we have some a priori knowledge that there is some difference in pediatric and adults, we would consider that as well. I can't really think of an example of that though, but that would be a factor.

DR. CHAN: Hi, Vicky Chan from DPV. I also wanted to address your question regarding probably general pediatric pharmacovigilance. So when we monitor products, sometimes we just, we don't know what the actual problem is, right?

We might start at a high level overview and say, "Wow, there's a lot of reports for lack of efficacy." Then we might take an entire cut of these reports and take a look at the age, country, dates that they were reported, and to see if there are any notable trends.

And if we do see that this is actually

reported higher in the pediatric population where it's not something that we expect, that's probably the path that we would go down and start to investigate, so I hope that addresses your question.

MEMBER JONES: Yes, so you do factor in age when you look at -

DR. CHAN: We do, definitely.

MEMBER JONES: Okay.

CHAIR DRACKER: Okay, Dr. Flick?

MEMBER FLICK: Forgive me, I guess I get a pass for being new, so I'll ask a couple of what might be not very intuitive questions. So the committee is being asked to address are there, do we agree there are no safety signals?

And that question addresses should the Agency undertake a closer examination of some signal that's come through adverse event reporting or should there be a change in labeling if I'm correct?

This is not labeled for under age 12, so if there were a signal that we found in

children under age 12, how would the Agency approach that since it's already not labeled and it already has a block box warning? So what would be the process that one would go through to address the use of this, the off--label use of the drug?

DR. ALEXANDER: So I can speak to that generally. I mean, typically, and as has been done here, if we've had clinical trials that have been done and were unable to establish that the drug was considered safe and effective in a particular population in the pediatric age group, we'd do what we've done, which is we've labeled the drug for the age group in which we have shown effectiveness in clinical trials and we've said that the safety and effectiveness has not been established for children under that age, and from the data that we had so far within those clinical trials, we didn't see a difference.

In the event that we did identify afterwards from postmarketing that off--label use was associated with an adverse reaction in a

population for whom the drug was not indicated, it in part depends on, one, the seriousness, how much of a concern that we have, and whether the risk that we identified could be mitigated by adding additional labeling.

But we have in certain instances added information about warnings for a population for whom the drug is not indicated because of the fact that we still continue to sort of see these types of adverse events that happen, and that does oftentimes help to then at least put out something that tells people that there is this problem if you try to use it in the way that it's being used off--label.

CHAIR DRACKER: Okay, Dr. Wade?

MEMBER WADE: Thank you.

DR. LEVIN: That would depend. It would be quite rare to - we have to have a very serious adverse event that we can really clearly link and probably do some quantization. It would have to be a very tight analysis to consider actually putting that, for lack of a better term,

maybe, you know, increased risk in a certain population.

So first of all, so, we don't - currently, it's kind of speculative. We don't right now have any such adverse event that we think is new in any way for the entire pediatric population, and we don't currently have adverse events that we think there's any evidence so far that there's a differential rate or risk within or between subpopulations of pediatric patients, so we really don't have that currently. There's nothing that we, as an Agency, are pursuing for -

MEMBER FLICK: No, so clearly you have two different systems. You have use data and you have event reports that come from two different sources which doesn't allow you to calculate a rate, so you don't really know what the rate is.

You have some ballpark estimate of rate, but that rate is dependent also on frequency of reporting -

DR. LEVIN: Yes, the numerator and denominator are -

MEMBER FLICK: - which we know is -

DR. LEVIN: - are very much in flux.

MEMBER FLICK: One would presume that in a seven-year-old, a report of a suicide would be a much higher rate of reporting in a younger child than you would see in an adult or an older child just simply because the rarity of those events would prompt reporting more frequently.

So the question gets to be: if you have a drug that's not labeled for use, and this is an off--label use in young children, and the committee sees some signal or believed it saw a signal, that would prompt you to do something, change the label, add a warning, or in all likelihood, study that in some way.

So the question would be is there a signal here or do we even have the capacity to know whether there's a signal in an off--label population like the seven to 12-year-old.

DR. LEVIN: Yeah, first getting back to the point, the first question being a sort of qualitative question, do we see in postmarketing

a particular type of adverse event?

The first thing to even trigger our concern would have to be a serious event. I mean, obviously suicide, you can't think of a more severe event really. It's hard to think about suicide in a child obviously, so those are severe events.

I think our first step would be - but even then, just like you said, it was a perfect point, what affects the numerator. The problem is the numerator as much as the denominator, maybe even more so, that there's all types of unconscious reporting biases or reasons people report severity, unexpectedness.

We have the really complex problem of while we know there's some increased risk of suicidality in the population, in pediatric patients, with certain behavior, there's also the therapeutic benefits in the population which we don't typically measure, which is hard to measure.

If the event is a high background

rate, depression, suicidality, it makes it so hard to know how to even think about the numerator much less the rate, but, yeah, the general point is if we had a qualitatively concerning adverse event that we thought would require more study, one way we look at our FAERS analyses, it's really hypothesis generating.

We can really never confirm, but we often do make decisions based on FAERS' reports. But I guess the answer is yes to your question. If we had some type of qualitative severe event that we thought was unusual, we could and would pursue that in various ways.

MEMBER FLICK: Forgive me, I'll make one more comment. So do you have a robust way to look at epidemiology, including calculating rates that is robust in children specifically?

DR. LEVIN: Probably no- is the best answer to that. What we would do to pursue this, you'd really - there's numerous, numerous ways to pursue, but we would consider existing epidemiological studies, literature.

We might consider asking the company to do a focused perspective trial. That's of course an option as well. We might use postmarketing databases such as Sentinel, which we're doing more and more. There's numerous ways to try to get at the question.

Using community-based exposure data is very, very tricky. You can get, I think as you suggested, like a rough handle on whether you might have a concern, but all of those types of analyses would be probably also hypothesis-generating rather than confirmatory.

MEMBER WADE: Thank you, Kelly Wade. I really appreciated this discussion about equivalence of exposure, both in terms of different formulations, generics versus class drug.

But I'm wondering since we're talking about the pediatric developing brain age six through adolescence, if there aren't age-dependent pharmacodynamic differences that affect both the efficacy of the drug, but also perhaps a

particular vulnerability in the developing brain to different exposures of the drug or its metabolites and if there's any information about age-dependent or pediatric brain development age-dependent pharmacodynamics in terms of either efficacy or potential toxicities?

Or really I guess I'm thinking about vulnerabilities of the younger, less developed brain to this class of drugs and whether or not that's formulation dependent, whether or not that's primary compound dependent, or generic versus class drug.

I just think what's the role of pharmacodynamics in the developing brain across this pediatric age spectrum and is that complicating our analysis?

DR. HAUSMAN: Ethan Hausman, I'll take a lateral stab at that and my comments are subordinate to the New Drug Review Division's and our toxicology people.

When drugs are developed in kids, we tend to collect a priori data that helps us feel

comfortable that it's safe to study a drug in children, so part of that is we get animal toxicology studies.

The data on the safety from the controlled trials is sort of the capstone. The effectiveness and the safety data is sort of the capstone of an entire development program for different age groups.

So we rely on animal data, but when you get to the phase three and you do a clinical study and it determines that safety and effectiveness have not been established, it's not necessarily that we don't get any safety information, but how we label things is an intricate process.

So we can look back to juvenile toxicology data, but in a drug that's not studied further down, we frequently don't have information, for example pharmacodynamics on a three-year-old. It just hasn't been studied.

So we can try to infer from animal data what effects there may be, but if it's not

being studied down in that age group, that information may not always get in the label.

DR. ALEXANDER: So I will add to that just that we recognize that there are a lot of intricacies and complications with regards to actually trying to evaluate the effectiveness of drugs, particularly for indications like depression, and schizophrenia, and other psychiatric effects.

The Division of Psychiatric Products is one of those places where we are typically requiring full-blown efficacy studies in the pediatric population because of the difficulty of being able to judge the effectiveness of the drug.

I haven't heard of a specific example of a drug where the pharmacodynamic differences were thought to play a role in whether the drug was effective or not.

I do think generally when we're looking at trying to judge what we think of in terms of whether a drug is expected to have a

pharmacodynamic effect, it's usually on the basis of looking at systemic exposures measured by blood concentrations, so whether there would be potentially a difference that could lead to less drug entering the brain to have an effect.

That's certainly a possibility, but at the end of the day, what we judge the effectiveness based on is what is ultimately seen as an effect in clinical trials on the clinical response of the patient.

And in this instance, for seven to 11-year-olds, regardless of whether it was related to pharmacodynamic effects or some other effect, we weren't able to demonstrate that the drug was effective and that's why it's labeled the way that it is.

CHAIR DRACKER: Dr. Sayej?

MEMBER SAYEJ: Thank you, Wael Sayej. I have a quick follow-up question to Dr. Jones' questions and I just want to make sure I understood this properly and I have a couple of comments after that.

When the bioequivalency tests are done by the generic company or on the generic drugs and compared to the brand name, are those studies done by the generic drug company or by the FDA directly?

DR. CHAZIN: No, they're done by the generic drug company as part of their application. What we were talking about is when we have a suspect drug, that we ourselves at FDA labs might test like if a formulation we find is not up to standards. There are a couple examples of these. We won't get into the Concerta example, but there are some that are publicly available.

They're rare and sometimes we can find a rare product whose formulation is not living up to the bioequivalence that was approved, so we'll find that out, retest it, and then ask the company to either withdraw it from the market or reformulate it.

So, and also one other thing is that FDA doesn't regulate the practice of medicine, so

a lot of these off--label uses, you have to remember, is we're kind of stuck with what we're talking about. We can only label the data we have.

We don't actually label for negative studies unless there's a true contraindication, so I think your question of the underage person being treated, it's hard to get at not just even a safety response, but at what we can put on the label when we don't regulate for off--label use, so getting at those questions.

DR. ALEXANDER: So I certainly agree with the comment that we don't regulate the practice of medicine. That is still up to individuals and there are plenty of examples of drugs that are used in adults as well as pediatric patients that are used off--label.

But the one place where we do actually sometimes include results of negative studies is in the pediatric population where we are actually authorized by Congress to include information and specifically to include results of negative

studies when they're available.

MEMBER SAYEJ: So my first comment is Dr. Hausman earlier mentioned one suicide in that age group under 12 is significant and we should look at it seriously, and I completely agree with that, and perhaps Dr. McGough can further comment on this.

A lot of these patients who have major depressive disorders already have suicidal ideation, and a lot of them probably have attempted some events of suicidal attempts and they do go on these medications.

So the cause and effect phenomenon can't be proven whether, you know, the medication is what's leading to these suicidal events or they already had these feelings to begin with.

And, you know, going through residency training and fellowship 10 years ago, 15 years ago, everyone said, "Oh, the medication just pushes you over the edge." Is there any truth to that or is there true cause and effect kind of correlation there?

MEMBER McGOUGH: So I need to be really clear. I think the event was suicidal ideation, but no behavior, right? So I think it's really important to make that clear.

And I have a lot of kids when their parents are saying, "Put your coat on," and they don't want to, or, "Do your homework," or that, they freak out and they have a temper tantrum and they say they want to kill themselves.

I mean, you know, and usually that's an event you have to help them, like they're caught in a corner and they don't know what else to do and they say they're going to jump out the window. That's a lot of the noise that's in here.

So I think there's a real difference between thinking this drug causes suicide, which has never been shown for any of these drugs, versus say, it causes leukemia in 60 percent of the people who take it.

So I would encourage people to realize there is a lot of background noise here with

terribly complex psychosocial situations, and parenting crises, and even the woman, you know, one woman, there was a 15-year-old who had PTSD.

She was probably - you know, I had a high school guy once. He was raped by his wrestling coach. To think that Prozac was going to help him with his issues is stupid, but that's what the insurance company, like, forced us to do.

So there's just a lot of noise here and I just very - I think ongoing monitoring is very appropriate and important, but I don't think there's anything new in terms of what we're hearing today.

MEMBER HOEHN: Can I just ask a clarifying question to what he just said?

CHAIR DRACKER: Sure.

MEMBER HOEHN: Sorry, my understanding is that we don't that what you said is true because they excluded all the deaths. So my initial question was that since they excluded all the deaths in the safety data, you do not know if

they excluded completed suicides, so I don't think that they know that information.

I totally agree with what you're saying about suicidality and the ideation, but my understanding from the FDA was since they excluded deaths from that analysis, they actually don't have that information.

DR. CHAN: Vicky Chan from DPV. So the deaths ended up being excluded from case series primarily because they were transplacental exposures. There were completed suicides, but because it is a labeled event, we didn't include those in our case series.

We focused on mainly the unlabeled, unexpected, serious adverse events in the pediatric population. There were also a few multidrug overdoses as well. That is just really difficult for us to determine the role of escitalopram in that case.

DR. STONE: Hi, I'm Marc Stone. Many of you may know me as the black box guy. Yeah, I think it is interesting when there is an allusion

to a case of suicidal ideation, which I think happens to be a 17-year-old, it becomes a question of, we start talking about completed suicides in seven-year-olds.

Yeah, it's a very big difference, and I think as you just pointed out, there's a lot of - it's totally conceivable, easily conceivable that an eight-year-old or a 10-year-old can think about, have the idea of killing themselves, can conceptualize it, but to actually focus a plan and to act on it is extremely unlikely.

Although again, if you look in the epidemiological, you know, the CDC epidemiological data, there are suicides in the six to 10-year-old age, although they're exceedingly rare.

And, you know, the information that we got from the analysis of clinical trials and this sort of age relatedness did seem to be increasing as they get, the development risk seems to increase as you go down in age.

But of course we're dealing with

extrapolations by the time you get down to six or eight, and you're also talking about a multiplication of effect, and even if it's a tenfold increase, it's a tenfold increase of something that's incredibly minuscule. So as a realistic risk, it's still exceedingly small.

In the clinical trials, there were cases of suicidal ideation in children under 10 which sort of supported that idea, but no cases of suicidal behavior, so, in the ones that were observed.

As far as some mentioned here about whether this is a question of pushing someone over the edge, that doesn't seem to be the case. It really looks more like when suicidal, treatment of emerging suicidal behavior that's drug related is an independent effect that has, that's unrelated to the underlying depression or much less related to the underlying depression and particularly in younger people.

For example, you see the same reductions in HAM-D scores in the young people

that attempted suicide as the young people who didn't attempt suicide on average, you know, so it probably has more to do with akathisia or something like that, that just creates an impulsive act of self-destructiveness that may not be related.

And in fact, the observed difference in suicidal behavior in young people in terms of relative risk was considerably larger in studies of things like anxiety rather than depression. So in major depression, we're seeing a countervailing, probably seeing a countervailing beneficial effect to go along with the toxic effect.

But I think it's important to conceive of this as an entirely separate kind of adverse event that just happens to have the same outcome as the worst-case scenario with the illness and indicative depression.

CHAIR DRACKER: Could you just mention your affiliation, please?

DR. STONE: I'm the Deputy Director

for Safety in the Division of Psychiatry Products.

CHAIR DRACKER: Thank you. We're getting tight on time, so Randi had a quick question and I think we may, unless it's really pressing, we're going to move on for a vote.

MEMBER OSTER: So I'd like to make some constructive inputs or what I would hope are constructive input. When we're looking at the suicide and the fact that those 74 were not included, I then want to look back at the words are in here about suicide that maybe will help us help families deal with this possible outcome. And on page six, it talks about that it should be monitored appropriately, but the definition of how you monitor appropriately and what families need to do is lacking.

And therefore when you go to page 24 of page 26 which is the FDA approved medication guide, the first question that I have is I don't know the reading level of this, but I wonder if it's the reading level of the families that need

to be monitoring appropriately, if this is enough information for them.

And specifically it talks about in section one, suicidal thoughts and actions, and what's identified here are negative, when the person feels worse, when they feel more agitated, and there have been some studies that have shown that sometimes right before someone does kill themselves, they're actually happy.

Because they've made a decision, they actually feel good, and that indication is not here that, you know, it could be that all of a sudden, my child is happy and then they kill themselves. So I don't know if there's enough information for parents to understand what they need to do.

I also want to just talk a little bit about on this medication guide, it says, "What should I avoid while taking Lexapro?" and we're talking about people that are under the age of 17, and it says that they shouldn't operate heavy duty vehicles.

I think we need to talk about that maybe they shouldn't be playing ice hockey, or maybe they shouldn't be going rollerblading. So I think it could be tied to the target market that we're looking at.

And then the last point I'd like to make is when we're looking at, you know, "What do I do?" the recommendation of "How do I get my - you know, I've had an event," it does give the 800 number for the FDA for the MedWatch.

We've already had very good reporting here about how few data we're getting from consumers, and it doesn't have the website, okay? And I did look up you do have a website, and so I would definitely advise that the website is added to this and to make sure that it's easy. Thank you.

CHAIR DRACKER: Thank you. Those are very useful. So we'll get ready for a vote. And I just want to comment that the whole issue of adolescent suicidal ideation and intent is very complicated.

I admit anywhere from two to four patients a week literally for children claiming they want to kill themselves. There's even websites that children now go on that want to end their lives. I mean, it's a very difficult issue which goes well beyond what we're discussing today.

So I think we're ready to consider the question. The FDA recommends to continue ongoing postmarketing safety monitoring. Does the Pediatric Advisory Committee concur? Let me go through the ground rules again with you.

We will be using an electronic voting system for this meeting. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will be then displayed on the screen. Marieann will read the vote from the screen into the record.

Next, we will go around the room and ask each individual who voted to state their name and vote into the record. You can also state the reason why you voted the way you did.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. If you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

MEMBER OSTER: Just, I'm the newbie. Just explain to me. FDA recommends continuing ongoing postmarketing safety, so if we vote yes, you will continue to do that, but if we vote no, what happens?

DR. LEVIN: You could, for example, after the voting, you could make, if you think it's not adequate, you make recommendations of further studies or further considerations, or Ethan, maybe you could comment on the general

approach to the question?

DR. ALEXANDER: Right, so the ongoing safety monitoring would still happen. It's whether you're voting no because of the fact that you want us to do something else specific with regards to this safety review.

MEMBER OSTER: Okay, thank you.

CHAIR DRACKER: I think that's a good demonstration of why new membership and fresh perspectives are important in this process, so thank you. So are we ready for a vote? Okay, let's all vote, please.

So again, you're voting to continue ongoing postmarketing safety monitoring. If you disagree, vote no, and then explain what you'd like to do as we go around the table.

Please, everyone press their buttons again, please, and vote the way you intend to. I screwed the process up by the way, so, just so you know.

(Pause.)

MS. BRILL: For the record, the

results are 11 yes, zero abstain, one no.

CHAIR DRACKER: Okay, Dr. Jones, if you, oh, you're nonvoting, is that correct? Okay, Dr. Flick?

MEMBER FLICK: I voted yes. There's clearly no significant signal for a new event. However, I would state that I think the fundamental problem that I tried to point out is that if there was a signal, there's very little capacity for the FDA to investigate that signal specifically in children.

So if we want to, if the goal here is to improve the safety, drug safety in children, we have to have robust means of being able to look for those rates and identify problems that we want to study.

So if you did see a signal, where would you go to investigate that more clearly within the Agency, not asking a sponsor to do it because you really have to do it yourself.

MEMBER SAYEJ: Wael Sayej, I voted yes. I do believe that we need to continue

monitoring. However, I would like to make a point that us pediatricians in general are at a major disadvantage because we are using these medications off-label and we're constantly fighting with insurance companies to get necessary medications approved for pediatric use.

I think it's about time that we make sure that these medications are tested properly in kids and have been shown to be safe and effective in kids as well before we start using them.

MEMBER TURER: Christy Turer, I voted yes, and I'd add that in these drug trials for kids, and I didn't talk about this before, but that we're really measuring the weight, the height, and the age and sex of these children. Many of the clinical trials that were done did not report those and so we have not been able to examine so much the impact on weight.

But I think we absolutely going forward should divide up the age groups more granularly and in line with the ages that these

are approved for, but outside of that, I think that ongoing monitoring makes sense.

MEMBER OSTER: I'm Randi Oster. I did vote no and the reason was I didn't feel we had enough data and that the data that we had we heard repeatedly was not enough or we didn't have enough answers for that.

And when we look at the 74 deaths and we look at the size of the population and our ability to collect valid information, I think there could be a lot more there, and therefore we need to - I'm happy that you will continue to monitor, but monitoring postmarket when the risk can be so significant I think caused me to vote no.

MEMBER WADE: Kelly Wade, I voted yes. I look forward to the ongoing evaluation and just would appreciate as much age-dependent granularity as we can have in the next review, and I would appreciate seeing the suicides even though I understand the resistance with the black box warning.

MEMBER CATALETTO: I voted yes primarily because we are asked to look at the group in which the drug is approved. The off-label use should be used as an impetus or an incentive to look at other children that are being studied in the younger age groups, but at this point, given the mandate that we have and the question that we have, I think that ongoing vigilance is appropriate.

MEMBER DiCAPUA: Peggy DiCapua and I voted yes mainly based on everything that I've read over the past two days.

MEMBER ANNE: Premchand Anne, I voted yes.

MEMBER CALLAHAN: David Callahan, I voted yes.

MEMBER McGOUGH: Dr. McGough, I voted yes and let me just make a very brief comment. People should be aware there is a rich literature that supports off-label use for these drugs. SSRIs are hugely effective in adolescent anxiety for example.

Companies may not want to pony up however billions it takes to get something on the label, but physicians are not acting blindly here. There is actually a lot of academically high level literature that supports the use of these medicines in these kids.

MEMBER HOEHN: Sarah Hoehn, I voted yes, but I would like to see for the next review more granularity around the age and I would like to see any completed suicides irrespective of the age, understanding there's a lot of compounding features, to have them included just so we can truly make an informed decision.

MEMBER HAVENS: Peter Havens, I voted yes.

CHAIR DRACKER: Okay, as a result of your excellent discussion, you've lost five minutes off your break, so we'll take a 10-minute break. I just want to remind all the members not to discuss any of the issues that we considered here this morning. Thank you. So we will adjourn, reconvene at 11:50. Thank you.

(Whereupon, the above-entitled matter went off the record at 11:39 a.m. and resumed at 11:55 a.m.)

CHAIR DRACKER: All right. We will start now. Dr. Taylor will start discussion on Intuniv, please. Thank you.

DR. TAYLOR: Hello, my name is Amy Taylor and I'm a medical officer in the Division of Pediatric and Maternal Health. I will be presenting the pediatric focus safety review for Intuniv (guanfacine ER).

This is an outline of my presentation. I will begin with some background information.

Intuniv or guanfacine extended release was first approved for marketing on September 2, 2009. It is a central alpha$_{2a}$ adrenergic receptor agonist.

On October 27, 1986 an immediate release guanfacine for management of hypertension was approved.

Intuniv is approved for the treatment of attention deficit hyperactivity disorder, or

ADHD, as monotherapy and as adjunctive therapy to stimulant medications.

Intuniv is contraindicated in people with a history of a hypersensitivity reaction to Intuniv or its ingredients. The warnings and precaution section of labeling includes warnings for hypotension, bradycardia, syncope, sedation, insomnolence, cardiac conduction abnormalities and rebound hypertension upon withdrawal of the product.

There have been two previous safety reviews of Intuniv by the PAC. The first was in May of 2011 which found no new safety concerns.

The second review was in September 2013 and it raised a concern for hallucinations as a safety signal. Hallucination was added as an adverse event to labeling in 2013.

Next I will be discussing the pediatric studies supporting Intuniv's indication.

Pediatric studies of Intuniv consist of five controlled monotherapy clinical trials,

one randomized withdrawal study, and one controlled adjunctive trial with psychostimulants in children and adolescents aged 6 to 17 years with ADHD.

Safety and effectiveness of Intuniv in patients less than 6 years have not been established.

There were two labeling changes that triggered this safety review by the PAC. The first was on November 19, 2014 when a new weight-based dosing regimen was added to the labeling.

The second was when information on maintenance treatment was added on March 18, 2015.

I will next discuss the drug use trends. This figure provides a nationally estimated number of patients who received a dispensed prescription for guanfacine ER from U.S. outpatient retail pharmacies from July 2011 through June 2017 annually.

The number of pediatric patients receiving guanfacine ER gradually increased from

approximately 420,000 in the 12-month period ending June 2012 to approximately 470,000 patients in the 12-month period ending June 2017.

Pediatric patients zero to 17 years accounted for approximately 90 percent of the total patients annually over the examined time period.

Of note, unique patient accounts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment from multiple products or over multiple periods of the study.

I will now discuss the safety review of FAERS reports. This table shows the total adult and pediatric FAERS reports from July 1, 2009 to May 31, 2017 with guanfacine ER.

There were 370 total crude count reports with 231 of them considered serious and there were 3 deaths.

For this safety review we will focus on the unlabeled U.S. serious pediatric cases.

There were a total of 169 U.S. pediatric reports with a serious outcome including 1 death. One hundred and thirty-six cases were reviewed and excluded from the case series if the adverse event was labeled, the case was unassessable, the adverse event was unlikely related to guanfacine ER, no adverse event was reported, the case was a duplicate, or the adverse event occurred prior to initiation of guanfacine ER.

So that leaves us with a case series of 33 pediatric cases including 1 death.

In this fatal case a 15-year-old female prescribed guanfacine ER 4mg per day and lisdexamfetamine 50mg per day for abnormal and impulsive behavior and disruptive behavior disorder.

She died at home from complications of portal and splenic vain~~vein~~ thrombosis.

Her past medical history included intellectual and developmental delay, congenital hypoplasia of corpus callosum, migraine, Crohn's disease, colitis and obesity.

Concomitant medications included propranolol.

She presented to the emergency department with abdominal pain and was found to be severely anemic. She received a transfusion and was discharged home with instructions for follow-up medical care. She died later that day.

The reporting physician stated that the thromboses were not related to the patient's medications but possibly due to a transfusion reaction.

In the next several slides I will present the remaining 32 cases of unlabeled serious adverse events. There were 23 cases with psychiatric adverse events. Nine of the cases contained aggression and self-injurious behavior. Six of the nine cases were confounded by the patient's medical history. One occurred after a missed dose of medication. Another after use of generic guanfacine, and one after an increase of the guanfacine from 1 to 2mg.

There were seven cases with adverse

events of suicide ideation, suicide attempt, or homicidal ideation. These cases reported a long latency to onset from the start of guanfacine and/or were confounded by concomitant medications.

There were three cases reporting paranoia, three cases reporting tics, and one case reporting the patient wanting to eat, fatigue and pain in legs and abdomen after discontinuing guanfacine.

Additional unlabeled serious adverse events reported were abnormal weight gain or weight increase, pancreatitis, a drug dispensing error in which Invega was dispensed instead of Intuniv, brain neoplasm, brain edema, blepharospasm and lichenoid drug eruptions.

This concludes the pediatric focused safety review of FAERS reports. No new safety signals were identified.

FDA recommends continuing routine ongoing post-marketing safety monitoring including monitoring for suicidal ideation and

behavior, pancreatitis, and medication error involving name confusion. Does the committee concur?

In conclusion I would like to thank the people listed on this slide for their help with this presentation.

CHAIR DRACKER: I just have a couple of questions first and then I'll allow everyone else. It's probably one of the few benefits from doing this job I guess is that I can speak first.

The first is that when we do clinical studies and we have adverse events we report adverse events whether the event itself is thought to be related to the drug or not.

That particular case, I would love to do a quality review on that case and see how the management occurred in the emergency room because there's a lot of missing issues there with regards to that, why she was transfused and why she had that thrombosis event. That's really more for the malpractice company to pursue rather than myself.

But, more importantly I didn't see a lot of reference made to things that I commonly experience with children taking Intuniv.

One is the severe lethargy and insomnolence that you see in these kids, and also the fatigue and the hypotension I sometimes pick up, probably the two most common things.

And to be very honest and transparent I don't report many of those findings because they're so frequent with that drug. So I just didn't know if you were looking at those signals as well.

MS. CHENG: Hi, this is Carmen Cheng. I'm the safety evaluator for this review from Division of Pharmacovigilance. And I did see these labeled events like the hypotension, decreased appetite, dizziness, decreased heart rate, hallucination, insomnolence.

And those were reviewed and excluded in our case series. So out of the 136 cases that were excluded the majority of them were because they were labeled adverse events and I did not

notice anything new or different from the labeling.

CHAIR DRACKER: Okay. I'm just telling you it's extremely common to see those effects. Usually when I have to change the dose or discontinue the therapy it's exactly for those complaints. That's why I wondered. Thank you.

I didn't monitor who had questions first so it's going to be on the honor system. So who raised their hand first? Go right ahead.

MEMBER TURER: Christy Turer. The thing that I would really value seeing on the label, the pediatric label, that we already know in adults is the impact on weight gain.

So for example, this is an alpha agonist, in the same class of drugs as clonidine. Clonidine was actually tested in the seventies and the eighties because of its known impact on appetite.

And they actually trialed it for treating anorexia. And we do see this clinically that when we place patients on clonidine and

guanfacine they get hungry.

The somnolence is absolutely true too. I actually missed that it wasn't on the label.

But when I look even in Lexicomp for the adult label of guanfacine it mentions weight gain on the order of 2 to 3 percent.

But you go to the neonatal Lexi drugs it's not there. It just mentions decreased appetite.

So I think for consistency and I think because clinically we're seeing this either they need to study this. And most of when I'm reviewing these trials they're reporting weight, they're excluding patients who are more than 200 pounds. They're not looking at BMI, BMI percentile.

So, I'm not sure how to guide us here but I think that it would at least make sense that the labels between adult and pediatric for this drug are consistent.

CHAIR DRACKER: I think the issue of concomitant drug therapy is also again very

important because there's a significant portion of these children who are on Intuniv who are also taking clonidine as a sleep aid. And we don't capture that information.

DR. STONE: Hi. I would just mention that when they do the phase 2 and 3 trials for guanfacine for ADHD you have a randomized controlled trial which they're measuring weight and can quantify any difference in weight gain between placebo and that would be in the label.

MEMBER TURER: Correct, but many of these trials. Same with the antidepressant trials. They're measuring weight. But in children you need weight indexed to height accounting for sex and age. You need BMI percentile. And that's what's not getting reported in many of these trials.

DR. STONE: That's also in the data at least for trials that are long enough where there's enough change in height to make a difference because otherwise you're just dividing by the same thing.

So if it's a six-month trial perhaps you'll see some differences based on growth spurts and the like.

MEMBER TURER: But it differs by age. So in any trials that include let's say 2- to 18-year-olds, or 6- to 18-year-olds you're going to have some adolescents who may not have height change whereas a 6-year-old is going to be on their peak height trajectory where it's going to change quite rapidly.

So I think because we need to have consistent measurement if we're talking about weight status and we're talking about adiposity weight alone isn't sufficient.

DR. STONE: Well, we do have BMI data. That's always calculated. In an adult trial you're not going to repeatedly measure people's heights but in a pediatric trial you do.

MEMBER TURER: Yes.

CHAIR DRACKER: Just one second. I just also want to mention that the other indication for Intuniv therapy is oppositional

defiant disorder in which the drug is used with other drugs, sometimes stimulants. So you get that counterbalance effect as well.

MEMBER CALLAHAN: David Callahan, child neurologist.

First, I have to confess I've used guanfacine off-label since the early nineties to treat kids with tic disorder and hyperactivity.

I think there's definitely a problem in some people with excessive weight gain. I've had several patients on guanfacine alone, parents report big weight gain. We've documented it. We've taken them off the drug and then maybe a year or two later we've tried it again because there aren't a lot of other similar drugs and we've seen the same thing happen in even a month or two, a short period of time.

And so I think we have enough information about the drug in adults and at least in my case clinical experience that we know that weight gain is seen in the small number of patients, not a large number.

And it's often hidden because many of the kids who take this drug are also on stimulants. So I think it needs to be looked at more carefully to see if it should be included in the label.

My second comment is the aggression and the irritability. I'd have to look back, I don't know if that's in the label or not but I warn all parents that some kids have the opposite reaction that we're looking for. We're looking for improved self-control and clearly some kids it makes them irritable and angry and aggressive. I see that on a frequent enough basis that I think it's a real side effect.

And I think you're seeing a signal for that. I think that occurs with other drugs we use to treat children with behavior and mood disorders too.

And so I think it's good that that should also be in the label if there is enough data to support that change.

MS. CHENG: This is Carmen. So in our

review we did have seven cases with aggression and one with aggression and self-injurious behavior.

The ones that I saw in my case series, they were mostly just confounded by the history so it's difficult to tell was it a truly new onset brought about by the drug. I guess compared to the other drugs that I monitor, the ADHD stimulants where some of the drugs are labeled for aggression, some are not.

It's always difficult to tease out the background history of the patient in these cases.

MEMBER CALLAHAN: I think there often is a background history of poor self-control. But when they see a clear worsening usually within a week of starting the drug and then you withdraw the drug and then things settle down when you remove it it's pretty clear that the drug can exacerbate aggression in some children, irritability and aggression.

MS. CHENG: And I don't remember -- I didn't note in my review that we did have -- only

with the increase in dose, I think that one case that seemed like it had a correlation. But the other cases were not so strong.

CHAIR DRACKER: Dr. Havens.

MEMBER HAVENS: Thank you. I just had a question of clarification on the statistical review.

Is the statistical reviewer -- can you handle those questions? Table 5 was really fascinating. It was sent to us.

It seems to suggest -- this is in the SPD503 study 315 which was for long-term benefit. Is this making sense to anybody? It was sent as a part of the packet. If we're not supposed to review it and talk about it then it's okay. But I just had a question. No?

DR. STONE: I wouldn't --

MEMBER HAVENS: It's on page 1224 in the -- we were sent the Cedar Intuniv Statistical Review. And table 5 says that in the treated group 50 percent had treatment failure and 50 percent didn't have treatment failure which

argues that it doesn't work long-term.

In the placebo group more had treatment failure so that's how it reached statistical significance. But table 6 which does a log rank test for the timing of the treatment failure, it seems to suggest that in the treated group they had a much shorter time to treatment failure than in the placebo group.

When we're looking for evidence of efficacy and it works half the time and it doesn't work half the time it was just interesting to see that. I wonder if there was comment from the statistician on how that was interpreted.

You can argue that fewer people failed in the placebo and since they were just failing being themselves it took them a longer time to get there.

PARTICIPANT: You're talking about the randomized withdrawal phase. I think the point you just made probably could explain at least partially what the finding was, that people who

had been effectively treated with active drug and then withdrew, they had a relatively -- for the group that relapsed it was relatively quick.

MEMBER HAVENS: This was -- they got the group, they put everybody on it. They only included people who seemed to have a measurable benefit and then they followed them out to see. They withdrew half and kept half on.

And the people who stayed on had failed half the time. Which doesn't speak to long-term benefit or argues against long-term benefit.

DR. HAUSMAN: Hi, Ethan Hausman. Just a quick clarification.

We pulled up a publicly available review and that table has been posted on the web.

MEMBER HAVENS: Maybe -- it's not the main focus here and I was just interested but it argues. One way to interpret the table is that in people continuing the drug over -- the average time to failure was 56 days even if you continued the drug.

And that half had failed by 56 days, whereas half had not. So I don't know if that -- it certainly argues for ongoing clinical review. I am supportive of what the FDA has --

DR. STONE: I mean, it may also depend on your definition of failure. When you're doing that kind of study in this case you might be looking for an event rather than.

MEMBER HAVENS: Well, right. Presumably a standardized event.

DR. STONE: -- even though the melt downs are --

MEMBER HAVENS: It's a standardized event that the drug did not seem to help half the time.

DR. STONE: That it's not 100 percent effective in preventing events.

MEMBER HAVENS: Okay, thank you.

CHAIR DRACKER: Yes.

DR. MCCUNE: I just wanted to just remind everyone certainly Dr. Dracker pointed out a number of adverse events that are labeled in

this population especially somnolence, hypotension and irritability are in the labeling.

And certainly the incidence of somnolence was 56 percent in the treated group so that would reflect your clinical findings.

CHAIR DRACKER: And that's clearly dose-related it seems in my experience anyway.

DR. STONE: And that is one interesting factor of the FAERS system and looking at sort of post-marketing events. When we see something that's common enough to be present in clinical trials we oftentimes don't get a lot of reports that would come to FAERS of those types of events specifically because it's so common and as identified in the labeling it's almost sort of a known factor and therefore they don't bother to report on something that's clearly known as an association with the drug.

CHAIR DRACKER: It's somewhat unfortunate because that data and information is still very important.

DR. MCCUNE: And just to follow up

that is reflected in the label as well in terms of the dose response.

CHAIR DRACKER: That's an example of good labeling.

MEMBER ANNE: Premchand Anne. In the safety and utilization review there was mention of two cases of pancreatitis where there is a possible role for guanfacine ER. And I think there is actually a physiological possibility here with the weight gain that's reported with this and the increased tendency to eat, the possibility of triglyceride elevation and potential for insulin resistance.

I think triglycerides, I don't know how often they are checked but triglycerides over 500, 500 to 1,000 could put the child at risk for pancreatitis.

I would consider -- one of my recommendations would be to consider checking a triglyceride level in these patients and if it's elevated we may need to rethink either adding fish oil or something to decrease the levels or

considering some other medication other than Intuniv.

CHAIR DRACKER: You know one of the core HEDIS quality indicators is monitoring metabolic -- doing metabolic studies on children on psychotropics on an annual basis.

And that's something that unfortunately many, many physicians don't do. So that's an important issue.

MEMBER ANNE: The AAP recommends this universal screening and everything between 9 and 11 years of age. And then if there's any other risk factors and so on and so forth. But only about 15-20 percent -- what is it, about 60 percent know about the guidelines but only 15 percent actually follow this.

So I think this is something that might be -- it should be considered to be added in the labeling perhaps.

CHAIR DRACKER: Randi, do you have anything to add?

MEMBER OSTER: Yes. So, again the

question no new safety signals were identified. And I just want to take a moment to go back to how we get the data.

And when we look at where the data is coming from, from the MedWatch that's 5 percent of the reports are coming from patients, consumers and healthcare professionals, and then the manufacturer is giving 95 percent of the reports.

I want to thank you for saying so clearly when you kicked this off I don't report things because it's so common and then Dr. Callahan sort of also -- he also sort of echoed that.

And not that I'm asking anyone to say how often even the doctors in this room are reporting, but just think about that. Do we have the data that could be identifying new safety signals.

And having said that when I look at 81 cases adverse event labeled and we had 81 but since it was already labeled we've excluded it.

Well, why isn't it clear? What's happening in the label that it's twice as many as how many we did look at?

So just because it has been labeled there's something going on there. And so we just need to look at the data from what we've even eliminated.

And then one of the things that I just want to bring up is we were looking at serious outcomes reviewed but yet we eliminated 10 of them because it was no adverse event reported.

And so then why is it here. We don't have the data to say why those 10 are.

And when we're looking at small numbers they become more important. And so my message is how do we get more data. How do we collect more data so it can be more valid.

And therefore when I look at what's in here on the label my comments are first of all I saw 25 percent were female. We're talking during the pediatric, during when they're young, and it talks about erectile dysfunction but what's the

impact on periods. I didn't see anything. Does it affect menstruation? I don't know.

But that's an important thing for a mother to know. I'm going to take this drug, I'm going to give this to my -- drug is it going to affect her period? I don't know. But a mother would be, from a mother's heart she would be thinking that.

And again the sports warning. They're not lifting heavy equipment but they are playing sports so we do need to look at that.

And also the things that haven't been studied that I believe should be on the label are things like the gastro illnesses and then renal impairment. Those are things people want to know, the harm.

So some of the information was in there but I didn't see it reflected on the label. Thank you.

CHAIR DRACKER: Thank you. Yes.

DR. HAUSMAN: Just a clarification or a little expansion on your very first comment.

I'm not going to address the rest of your comments which are all very good and we take to heart.

The excluded cases. They are reviewed, OSE reviews them before they decide whether to keep them in the case series that's presented to you.

And part of that review is -- and if there are perceived changes in the frequency or severity they're not excluded, they're included. So even if it is already labeled it's not just that something is labeled so it's not looked at and it's not addressed.

So I just wanted to make that clear for the new members of the PAC that they're not -- oh it's labeled, I'm not even going to read it anymore. It's read, it's digested, a safety evaluator and possibly their team leader looks at the report and says okay, it's already labeled. Does this reach a bar that we have that we want to include it in the review or not. So it's not just that it's put in a pile and not looked at.

CHAIR DRACKER: That's important to state because I think the perception might have been because it's in the label it's just overlooked. So I think that's critically important. Thank you.

Anyone else? Yes.

MEMBER ANNE: Just going back to my point about the pancreatitis I did a search in the actual label and it was not mentioned. Granted it's only two cases, but it wasn't mentioned. And that can be fatal obviously.

DR. ALEXANDER: Understood and we appreciate your comments. I think that that is a message that we can take back that we should look at whether pancreatitis should be -- whether we have other cases besides the ones that were identified within the review in other populations with this drug and whether there should be more in the labeling with regard to pancreatitis.

CHAIR DRACKER: So I understand the process. You go back to the manufacturer and ask them if they have any other indicators?

MS. CHENG: So actually I can elaborate on it.

So we did highlight the two cases of pancreatitis that we were concerned about. So as part of this review I did expand on a search even to adults through the whole database until the search date and I reviewed those cases. There were eight additional cases and the majority of them provided very little information for assessment.

And this review at the time we searched through August 2017. So we've been monitoring the cases and I have not identified any new cases with the same search since the review has been done.

So we don't have any major concerns. But we are keeping an extra eye on pancreatitis if we do get good cases that come up.

CHAIR DRACKER: And that is one of the recommendations as well for monitoring.

MEMBER ANNE: I think considering adding the triglyceride level to the label, or

advising the pediatricians to do this I think may not be a bad idea. You tend to see these things elevated in the pancreatitis situation.

DR. STONE: I would think you're adding quite a long chain of connections here. First, you're assuming the pancreatitis was due to the drug. Secondly, you're assuming that the pancreatitis that did occur was due to elevated triglyceride levels and there are lots of other reasons for that.

So I think we'd have to establish a little stronger chain of causation before we make a recommendation like that. We do have data from clinical trials that do measure triglyceride levels and there was no marked difference between drug and placebo otherwise that would be labeled.

MEMBER WADE: Just to follow up on that I think it would be helpful when this kind of diagnosis comes up such as pancreatitis if you could go back into the clinical trials that were performed that led to the label, if you could just give us -- I'm sure you've gone back to them

-- to say what we know about pancreatitis from the original phase 3 trials is that the trials looked at these specific laboratory tests and this was the two groups.

Because it could be that laboratory values for pancreatitis were not collected and therefore we don't have them, or there were incomplete laboratory assessments on a certain number of patients.

Or it could be that those trials actually collected really excellent labs related to pancreatitis and we actually know there was no difference in the placebo group versus the drug group.

This is kind of an example where I think going back into that data that you have and showing us what we actually know from the randomized controlled trials would be helpful.

DR. STONE: I do take your point and we do measure things like triglycerides. For a case of pancreatitis, pancreatitis is more of an all or nothing. It's not quite the same thing as

being a little bit pregnant but if you were to measure for example amylase levels the fact that there was a slightly higher amylase level with drug rather than placebo.

First of all, it's unlikely we'd detect it but even if it were the case it would probably not be a marker for clinical pancreatitis. The issue is whether there were cases of pancreatitis in the clinical trial given that there are just two reported cases among hundreds of thousands or millions of people who have taken these drugs. The incidence is likely extremely low and not going to show up in a clinical trial.

That's the problem we always face with trying to evaluate safety initially in a clinical trial.

CHAIR DRACKER: Anyone else? Yes.

MEMBER FLICK: So I just want to reinforce a little bit. So what we have are two cases out of many, many thousands with no comparator.

So we really don't have a rate and we don't have a comparator. So what is the frequency of pancreatitis in the population not taking this medication. It may be higher, I don't know.

And then the flip side of this is if we were to ask to have that label changed to ask for metabolic testing we have to consider the imposed cost.

So now you're going to test literally tens of thousands of people at a cost that's extraordinary trying to find a very few cases that may actually be similar to the frequency within the population.

So the ability to detect a true positive in that would be extraordinarily low and the cost would be extraordinarily high to detect each one of those true positives.

So from an epidemiologic standpoint it doesn't make sense unless you have better data that would help you'd rive that.

Randomized controlled trials or the

kinds of studies that are done for approval are never large enough to pick up these kinds of events although you might -- I would maybe differ with you and say that if you had an elevation of amylase even slightly above what you see in the control group that would tend to make you want to look at this more closely even though you didn't have pancreatitis.

MEMBER SAYEJ: I would just like to add one more point to what was just said. And I completely agree with the statement.

We can't be digging for one case amongst millions of patients who are taking it. These kids who have had pancreatitis most likely have had triglyceride levels checked when they were diagnosed with the pancreatitis and it would be worthwhile to go back and look at those cases specifically and see if there was any specific cause for the pancreatitis.

Most of the time pancreatitis in pediatrics is idiopathic. We have no identifiable cause. Whether it's a viral illness

or medication most of the time there's no identifiable cause.

So I wouldn't rush into trying to change the label to add the pancreatitis or to request for any additional testing. I do agree with continued monitoring and keeping an eye on this.

CHAIR DRACKER: Anyone else. Dr. Havens, do you have anything else?

MEMBER HAVENS: No, but thank you for asking.

CHAIR DRACKER: You're welcome. All right, are we ready for a vote? And I assume the medication error involving name confusion is specific to guaifenesin, correct.

MS. CHENG: I'm sorry?

CHAIR DRACKER: The medication error involving name confusion is specific to guaifenesin?

MS. CHENG: Yes. This would be for Intuniv and Invega that we saw specifically.

CHAIR DRACKER: Intuniv and what, I'm

sorry?

MS. CHENG: Intuniv and Invega. These were the cases that we saw.

CHAIR DRACKER: All right. Yes.

MEMBER TURER: Christy Turer. May I ask for a clarification.

If we vote routine monitoring can we separately vote to add something to the label, or by saying we agree with routine monitoring we're negating the ability to add something to the label.

CHAIR DRACKER: I think that's a separate issue altogether but I'll let them.

DR. ALEXANDER: You can still go ahead and vote yes but make a recommendation if you want something added.

CHAIR DRACKER: So you would have an opportunity to do that after you vote and we go around the table. All right.

Shall we take a vote? I'll read the question. FDA recommends continuing routine ongoing post-marketing safety monitoring

including monitoring for suicidal ideation and behavior, pancreatitis and medication error involving name confusion. Does the committee concur? Please make your vote.

Who did not vote. We're okay. Okay, good.

MS. BRILL: Okay, for the record the results are 11 yes, zero abstain, and 1 no.

CHAIR DRACKER: Peter, we're going to start with you.

MEMBER HAVENS: Peter Havens. I voted yes.

MEMBER HOEHN: Sarah Hoehn. I voted yes. And I do agree to look into the pancreatitis more to see if there's anything there.

MEMBER MCGOUGH: James McGough. I voted yes.

MEMBER CALLAHAN: David Callahan. I voted yes. I recommend adding weight gain to the signals to watch.

MEMBER ANNE: Premchand Anne, yes.

MEMBER DICAPUA: Peggy DiCapua, yes.

MEMBER CATALETTO: Mary Cataletto, yes.

MEMBER WADE: Kelly Wade, yes.

MEMBER OSTER: Randi Oster, no. I would like to say that the data exists in the market and I'm hoping that we see the ability for us to try to get more data so when we have these discussions we can feel that we have more data points that we're evaluating.

I also would like to say that the points I made earlier about what I feel should be on the label regarding the sports should be added. Thank you.

MEMBER TURER: Christy Turer. I voted yes. I would like weight gain added to the label.

I'd also want to know with the cases of pancreatitis if they occurred in children with existing obesity. Because in those children we are supposed to be checking for lipids a minimum of every two years and hopefully we'll have

safety systems in place to be able to do that.

One I guess question is whether we're going to be incorporating data from Sentinel, not just FAERS into these reviews but that can be dealt with later.

MEMBER SAYEJ: I voted yes and I will make a couple of comments.

I think the standard of care is a little bit different from what the label should say in many cases.

So if we're treating patients with these medications as pediatricians in general we should be aware of what the possible side effects are.

Yes, one case out of a million is not probably going to be labeled but something that should be part of the general practice in terms of clinical guidelines. Those are the things that will guide us in terms of what we test.

We had this conversation a couple of years ago about general guidelines and standard of care.

The second comment I would like to make is the one cause of death that we really never got to talk about it, I certainly agree with Dr. Dracker about that patient had a lot of issues going on.

Patients with Crohn's disease and colitis also have a hypercoagulable state and are more prone to develop portal vein thrombosis, splenic splenosis just from the inflammatory process.

So there's certainly no evidence of cause and effect with the medication.

MEMBER FLICK: Randall Flick. I voted yes.

CHAIR DRACKER: Okay. We will have a lunch break. We will reconvene at 1:30. Marieann needs to say a few things.

I just want to remind everyone to please don't discuss the proceedings we've had this morning. Thank you.

MS. BRILL: A few announcements. For the panel members the breakout room is in 1404.

I was asked to say that if you ordered and paid for your lunch your lunch boxes should be in 1404. Thank you so much.

(Whereupon, the above-entitled matter went off the record at 12:41 p.m. and resumed at 1:32 p.m.)

CHAIR DRACKER: Okay. We will start the afternoon session. Marieann has an announcement first.

MS. BRILL: I am so sorry I have so many announcements today, but I was informed that the corrected slides for Lexapro are given to, I guess, our PAC members. Okay. And then David's slides will be posted on the website within 48 hours, or let's just say next week. Thank you.

CHAIR DRACKER: Thank you, Marieann. We now have the FDA presentation on the summary of FDA completed review of pediatric safety issues and updated labeling for Exjade.

DR. WALDRON: Good afternoon. My name is Peter Waldron. I'm a pediatric hematologist in the Office of Surveillance and Epidemiology,

and I'm the team leader for the Pediatric Safety Evaluation of deferasirox.

First, I will provide some background for the Committee, then I will present the Division of Pharmacovigilance's findings from the FDA Adverse Reporting System, or FAERS, and the literature. Then each of these groups will present their findings of this safety evaluation. I will also provide a summary at the end.

deferasirox was approved for marketing in 2005 under the trade name Exjade for the indication of transfusional iron overload for ages two years and older. In 2009, the maximum dose was increased from 30 milligrams to 40 milligrams for patients not adequately controlled with doses of 30 ml/kg per day.

In 2010, a box warning was added for renal failure, hepatic failure, and gastrointestinal hemorrhage. In 2013, Exjade received an additional indication for patients ages ten and older with non-transfusion-dependent thalassemia and chronic iron overload. For this

indication, a maximum dose of 20 ml/kg per day was specified.

In 2015, a new dose form of deferasirox, a filmcoated tablet, was approved under the trade name Jadenu. And in 2017, a granular form of Jadenu was approved. Due to increased bioavailability of the Jadenu form, a 7 milligram dose of Jadenu is equivalent to 10 milligrams of Exjade.

In 2015, January, two years after the approval of the new indication for non-transfusion-dependent thalassemia for ages ten and older, a pediatric-focused safety review was performed. The findings of the review were presented to the PAC in September 2015.

One of the cases presented was of a child from the U.S. with a fatal outcome. She was a 35-month-old girl with transfusion-dependent thalassemia who started transfusion at age seven months. She began chelation with Exjade at age 24 months. Her concomitant medications were multiple vitamins, vitamin D,

and folic acid.

She was receiving a dose of Exjade greater than 30 ml/kg per day when her serum ferritin was less than 1,000 micrograms per liter. Her history indicated that she was at risk for acute hypovolemia due to diarrhea, vomiting, and possibly decreased oral intake, in addition to fever and association with a documented RSV infection.

She presented with acute kidney injury as indicated by serum creatinine value five times her baseline value and oliguria, as well as liver failure indicated by encephalopathy and coagulopathy. Later, she developed avert shock and respiratory failure. She died due to cerebral herniation.

During the public testimony at the September 2015 Pediatric Advisory Committee, the mother of the child who died gave testimony on her experience. Then a representative of the Cooley’s Anemia Foundation testified about the membership's concern for use of Exjade during

febrile illnesses and requested that a warning be added to the product information to stop the use of Exjade for children who develop a fever.

In November 2015, the Division of Pharmacovigilance was consulted based on the request from the PAC "to acquire any data regarding safety of continued medication to children who have fever and report back to the Committee." In April 2016, a tracked safety issued was open to facilitate participation of multiple disciplines within FDA to evaluate this safety concern.

In March 2017, I presented an interim report to the Committee. And in April 2018, the safety evaluation was complete. In May of this year, the deferasirox labels were updated.

The FDA staff who became involved in this safety issue were moved by the death of this child. At the same time, we were optimistic that we could improve the safe use of this drug among children, but, first, we needed to analyze the available data and perform additional analyses to

develop the evidence necessary to support changes to the label.

These are the questions that we sought to answer in our effort to improve the safe use of deferasirox: Are there features of childhood illnesses, such as hypovolemia, that could interact with deferasirox use to produce severe toxicity? Could continued drug use during periods of decreased glomerular function result in increased drug exposure? And is there an interaction between drug dose and body iron burden such that, at a high body iron burden, a given dose may be associated with a lower rate of adverse actions, whereas that same dose at a lower body iron burden will be associated with an increased rate of adverse reactions?

Now I will present the Division of Pharmacovigilance's findings from FAERS and the medical literature for these safety concerns. You will note that the safety team expanded our evaluation beyond fever. Fever is a common event in the pediatric age group. As I presented in

the interim report to the PAC in March 2017, we had evaluated clinical trial data and the literature and we found no support for an association between fever alone and any specific adverse event.

The safety team is very grateful to the family of the young girl who died for allowing us access to her medical records. That information, in combination with knowledge of pediatric illnesses and the known safety profile of deferasirox, guided our analyses to include dehydration or hypovolemia events in our evaluation.

This slide describes the well-known limitations of any database of spontaneous reports. Since you all have copies of the slides, I will spare you my reading of them.

This table is a summary of the findings of a FAERS search. All reports with an adverse event associated with deferasirox use were searched for reports with preferred terms associated with fever or dehydration. Then we

reviewed the individual narratives to ensure that the case reported fever or hypovolemia. Those 149 cases, confirmed cases, were then reviewed to determine which cases reported features indicating renal impairment. The most commonly reported indicators of renal impairment were serum creatinine elevation and proteinuria.

The median age of the 149 cases was eight years. Fifty-eight cases that reported fever only had the lowest rate of renal impairment, five percent. The 68 cases which reported only dehydration had a 25-percent rate of renal impairment, and the 23 cases which reported fever and dehydration had a 48-percent% rate of indicators of renal impairment. These findings indicate a considerable rate of indicators of renal impairment with typical features of childhood illnesses.

In addition, the association between the severity of the risk factors for hypovolemia and the increased frequency of renal impairment suggest a dose effect of hypovolemia risk factors

for indicators of renal impairment.

This table summarizes the findings of another FAERS search and literature reports of acute hepatic failure or hyperammonemia in children receive Exjade. Hepatic failure was defined as a case with a report of biochemical indicators of liver injury and mental status changes. Subsequently, cases were also characterized based on indicators of coagulation system function and on the presence of indicators of acute kidney injury, hypovolemia, and over-chelation.

The table includes thirteen FAERS reports and three literature cases which were not in the FAERS database at the time of the FAERS search. The median age of this group was five years, and the range was two years to fifteen years. One case did not report age. All FAERS reports describe findings of encephalopathy and four reported findings of coagulopathy. Two of the literature cases reported encephalopathy and all reported coagulopathy. Seven reports did not

provide data that allow characterization of the coagulation system.

Cases that reported a prothrombin time greater than or equal to 30 seconds, an INR value greater than or equal to 2.0, or administration of plasma for coagulopathy were interpreted to demonstrate coagulopathy. Ten of the thirteen FAERS reports and two of the three literature reports described indicators of acute kidney injury. Cases that reported doubling of baseline serum creatinine, a statement of renal failure, or a report of renal replacement therapy were interpreted to demonstrate acute kidney injury.

All cases that reported criteria that allowed evaluation of risks for hypovolemia had that finding. Cases were interpreted to have risks for hypovolemia if they reported vomiting, diarrhea, or at least one day of anorexia.

Seven of the thirteen FAERS reports and all three of the literature reports described over-chelation. Six FAERS reports did not allow

characterization of this criteria.

A report was interpreted to indicate over-chelation when the patient was receiving a dose of Exjade of greater than 25 ml/kg per day at a time when the serum ferritin was less than 1,000 or a dose of Exjade greater than 20 milligrams, sorry, greater than or equal to 20 ml/kg per day at a time when the serum ferritin value was less than 500 micrograms per liter or a statement of discontinuation of all chelation following resolution of the acute event.

In summary, the DPV analysis found a high frequency of indicators of renal impairment among children with risk events for dehydration with or without fever and an association between risk factors for hypovolemia and the incidence of renal impairment indicators. Among the acute hepatic failure cases, most cases were characterized by severe acute kidney injury, risk factors for hypovolemia, and over-chelation.

The next speaker is Dr. Okusanya from the Office of Clinical Pharmacology who will

discuss their findings of the interaction between renal function -- I don't know what happened. Okay. I didn't hit escape one time, but okay. He will be followed by Dr. Khurana, a pediatric nephrologist from the Division of Pediatric and Maternal Health, who will describe their evaluations of clinical methods for assessment of renal function and the application of those findings to d

deferasirox dosing and monitoring during treatment. Last, Drs. Bird and Gelperin, who are members of the Division of Epidemiology, will report on their findings from clinical trial data. These reports include a nested case control study which evaluated the effects of Exjade dose and serum ferritin on the likelihood of acute kidney injury and findings from the sponsor's five-year registry which included children who were ages two to five at study initiation.

Dr. Okusanya.

DR. OKUSANYA: Thank you very much.

Good afternoon. My name is Lanre Okusanya, and I'm a clinical pharmacologist with the Division of Clinical Pharmacology V.

The Office of Clinical Pharmacology was consulted by the Division of Pharmacovigilance to help answer a few questions that arose during the deferasirox pediatric-focus safety evaluation. In this presentation, I will focus on two specific questions: one, what is the impact of deferasirox use on renal function; and, two, is there an exposure response relationship between deferasirox exposure and renal injury?

As mentioned by Dr. Waldron, several cases of renal dysfunction, including failure, has been observed in patients taking deferasirox. As such, a box warning was placed on the label in January of 2010. As part of the box warning, a close patient monitoring is required, especially in patients with underlying renal disease.

Now, while we note that the elevation of serum creatinine patients on deferasirox is

not uncommon, reversible decline in true renal function has been observed in children, as described by Dubourg, et al. And it showed that a decrease of approximately 20 percent, they showed it at approximately 20 percent in glomerular filtration rates, even in patients with normal renal function.

Now, despite the fact that deferasirox and its metabolites are primarily excreted by feces, renal impairment has an impact on deferasirox exposure. A comparison of the dose-normalized trough clearance in adult patients with varying degrees of renal impairment to those with normal renal function at week 13 and week 49 of study US03, a single-arm trial in patients with myelodysplastic syndrome as shown in the figure above. We can see that there is a numeric increase in the dose-normalized trough concentrations with declining renal function, suggesting that patients with poor renal function may have higher deferasirox concentrations.

This impact of renal function of

deferasirox concentration was also evaluated in pediatric patients using data provided by the sponsor from three different studies. This was evaluated using a linear mixed-effects model where eGFR, the estimated glomerular filtration rates as calculated using Schwartz equation was related to the log-transformed dose-normalized trough concentration. The impact of age, body surface area, underlying disease, gender, and race were also evaluated in the model.

The model showed a decline in eGFR was associated with increase in dose-normalized trough concentrations. For example, following a three-percent decrease in eGFR from 120 ml/min to 80 ml/min, a 29-percent increase in trough concentration is predicted.

In addition to eGFR, body surface area was also a significant covariate, indicating that patients with small body surface areas had higher dose-normalized concentrations than patients with larger body surface areas. As such, a small change in eGFR in patients with small body

surface areas is predicted to result in higher absolute trough concentrations in patients with higher body surface area.

Now, to further explore the clinical relevance of these increases in exposure, a relationship between deferasirox concentration and the probability of renal injury was explored. The relationship between drug exposure and the probability of varying levels of renal injury were evaluated by the sponsor using the proportional odds model. The model modeled the odds of a patient worsening, that is the odds the patient worsening in their renal function or resulting in renal injury.

Now, the following renal injury categories were assessed: One, a greater than 25-percent increase in serum creatinine or urine protein-to-creatinine ratio grade on this line. Two, a greater or equal to 33-percent increase in serum creatinine or urine protein-to-creatinine ratio greater than 0.4. And, three, a serum creatinine greater than the upper limit of normal

or urine protein-to-creatinine ratio greater than 0.6.

Now, the analysis revealed a relationship between predicted trough concentrations and the risk for renal injury. Baseline elevation in serum creatinine, disease type, and time from the start of treatment were also found to be statistically-significant covariates. What was found was that a twofold increase in the trough concentrations, following a twofold increase in trough concentration, the estimated probability of patients' renal functions worsening was 1.52.

In summary, based on this analysis, we can conclude that deferasirox can cause renal injury. This is reflected in the black box warning that is currently on the label. Decreases in renal function can lead to increases in deferasirox concentrations, and higher deferasirox concentrations for an extended period of time can increase the probability of renal injury. This data is supportive of the findings

to be presented by Dr. Bird and Dr. Gelperin.

DR. KHURANA: So one of our goals as part of the tracked safety issue was to identify areas where existing labeling language could be updated or strengthened to enhance the safety of deferasirox use in pediatric patients, especially those down to two years of age given the discussions at the 2015 PAC meeting about the index case. I'll be talking about the renal considerations we discussed when planning the safety analyses, which ultimately led to the deferasirox labeling changes which were implemented earlier this year.

This is the outline for my presentation. I'll briefly touch on the spectrum of renal toxicity reported with deferasirox use in both adults and pediatric patients. I'll then go into some of the challenges with monitoring of renal function that we considered when planning the analyses conducted by our safety evaluators, and I'll focus on the difficulties with relying on serum creatinine and creatinine clearance to

guide drug dosing decisions and the utility and limitations of using prediction equations to estimate GFR. I'll end by highlighting the updated renal dosing and monitoring recommendations added to deferasirox labeling earlier this year as a result of our safety analyses.

So in pre-marketing clinical trials, transient elevations in serum creatinine and proteinuria were the most common renal adverse events reported. Post-marketing reports have subsequently described renal proximal tubular dysfunction and acute kidney injury of varying severity.

deferasirox is a known renal proximal tubular toxin, and the ensuing laboratory abnormalities really depend on the extent of tubular injury. Tubular injury can range from an isolated defect in one particular transporter to a global breakdown in solutransport known as the Fanconi syndrome.

And you can see from this slide that

measurement of serum creatinine would not capture this type of tubular injury. So unless prescribers are actively monitoring their patients for these abnormalities, deferasirox-associated renal tubular toxicity could go undiagnosed.

So what are some of the challenges with monitoring renal function in the context of drug dosing? In current clinical practice, increases in serum creatinine and decreases in urine output over a short time frame are used to diagnose and stage acute kidney injury in both adults and pediatric patients. However, serum creatinine is known to be an insensitive marker of early renal injury, which makes reliance on acute changes in serum creatinine alone problematic from a dosing perspective, especially for drugs with a low therapeutic index.

You can see from this figure that a small increase in serum creatinine is initially associated with a large drop in GFR. And because of this relationship, waiting for the serum

creatinine to increase by a certain percentage before reducing the dose or to greater than the upper limit of normal for age before interrupting the dose for a given drug may be too late if the goal is to prevent drug-related toxicity.

Another important limitation to the use of serum creatinine is the substantial intra- and interindividual variability typically seen with serum values.

Accurate interpretation of the serum creatinine is further complicated by the fact that normal values vary not only by sex and age but also by the type of serum creatinine assay used. Hopefully, you can see from this table that a value of 1 mg/dL derived by the enzymatic method would be considered the upper limit of normal for a 15 year-old boy but would exceed the upper limit of normal for a 15 year-old girl and would be two times the upper limit of normal for a five year-old boy.

Creatinine clearance has traditionally been used to estimate renal function, but it's

important to note that creatinine clearance is not synonymous with GFR. Creatinine clearance is based on urinary creatinine which is not only filtered by the glomeruli but also secreted by the proximal renal tubule. And as a result, creatinine clearance values overestimate true GFR by that fraction of urinary creatinine that is derived from tubular secretion.

FDA has historically used the Cockcroft-Gault equation to estimate creatinine clearance for use in pharmacokinetic studies to determine drug dosing in adults with renal disease. The resulting values are expressed in ml/min and should be corrected for body surface area before being applied to pediatric patients.

Serum creatinine-based prediction equations are increasingly being used to overcome the interindividual variability associated with serum creatinine concentrations. These equations incorporate key demographic and clinical variables to account for variation in creatinine production among individuals. The MDRD and,

increasingly, the CKD-EPI equations are used to estimate GFR in adults while the Schwartz equations are widely used to estimate GFR in children.

The Schwartz equation was originally developed in 1976 to estimate GFR in children and relied on an older, less precise method for assaying serum creatinine. The equation was updated in 2009 to be used with standardized creatinine methods. Both equations rely on serum creatinine, height, and an empirical constant to estimate GFR corrected for body surface area in children.

The utility of any prediction equation really depends on how well the estimated GFR value corresponds to true GFR in the population of interest. This figure shows mean measured GFR values corrected for body surface area in otherwise healthy children with mature renal function. And in general, measured values greater than 90 are considered to be normal.

Although the Schwartz equations are

commonly used to estimate GFR in children, these equations are not perfect and have limitations which must be considered when interpreting the eGFR values. Like other creatinine-based prediction equations, the Schwartz equations don't account for interindividual variability in creatinine production due to volume status, activity, and dietary protein consumption. They assume that serum creatinine is at steady state, which is not the case in the setting of acute kidney injury.

And, finally, it's also important to know that the updated Schwartz equation was developed in a pediatric chronic kidney disease population, so more data are still needed on how well this equation correlates with true GFR in children with more normal renal function.

The baseline serum creatinine concentration for any given individual represents a steady state when daily creatinine production equals daily urinary creatinine excretion. eGFR values derived from the Schwartz equations can

over or underestimate true GFR if the baseline serum creatinine is impacted by factors which can tip this balance in any one direction. Overestimation of true GFR is a possibility for patients with low baseline serum creatinine values. These patients have lower than normal daily creatinine production due to reduced muscle mass or malnutrition from their underlying disease.

Underestimation of true GFR is possible when there's some other reason for the baseline serum creatinine to be elevated. And, finally, chronic anemia can induce changes in renal blood flow that can actually increase GFR, so it's unclear how well eGFR corresponds with true GFR in the thalassemia population in whom chronic anemia is likely to be highly prevalent.

We applied many of the concepts I've just shared with you in planning and conducting the analyses you've heard and will hear from our safety evaluators. Because the goal of our safety analyses was to inform drug dosing in

product labeling, we've relied on eGFR values derived from the Schwartz equations as the basis for the exposure response analyses and the analysis of the Five-Year Pediatric Registry, as well as to define cases and controls in the nested case control study.

Based on our safety analyses, we identified several areas where labeling could be updated to mitigate the risk of renal toxicity in pediatric patients, and I'll briefly highlight some of these areas in my remaining slides.

As Dr. Waldron mentioned, post-marketing reports prompted FDA to add a box warning to deferasirox labeling in 2010. The box warning cautioned prescribers about the possibility of acute renal failure and death with product use, particularly in patients with co-morbidities, and recommended dosage adjustments based on changes in serum creatinine.

The box warning was updated earlier this year to emphasize reliance on changes in eGFR to guide drug-dosing decisions and more

frequent monitoring and increased vigilance of patients with baseline renal impairment or with one or more risk factors for acute kidney injury, including pediatric patients with volume depletion or over-chelation.

Prior labeling language contraindicated product use in patients whose serum creatinine was more than two times the upper limit of normal or who had a creatinine clearance less than 40. Updated labeling now contraindicates use in all patients two years of age and older with an eGFR less than 40. Prior labeling informed prescribers to initiate therapy based on serum creatinine and creatinine clearance and to reduce the starting dose by 50 percent in patients with baseline renal impairment as defined by creatinine clearance.

Updated labeling provides initial dosing recommendations based on eGFR derived from age-appropriate prediction equations and includes language informing prescribers to look for both tubular and glomerular dysfunction prior to

initiating therapy. Current labeling also includes more detailed language about dose interruption in pediatric patients with volume depletion due to an acute intercurrent illness, as well as the importance of continued monitoring of tubular and glomerular function during therapy, and to reevaluate the risk-benefit profile of continued deferasirox use in the presence of either type of renal injury.

I'd like to acknowledge these members of the Division of Pediatric and Maternal Health who helped me with this presentation. Thank you.

DR. BIRD: I'm going to be giving a presentation on analysis of pediatric clinical trial data.

So through an information request to Novartis, clinical study data sets were obtained for deferasirox-treated pediatric patients. The pooled clinical data sets included company-sponsored interventional and perspective observational clinical studies. Ten studies were identified that included pediatric patients with

perspective collection of clinical laboratory data and all data presented here for Exjade because the pooled clinical trial data sets contained very few patients receiving Jadenu for transfusion-dependent thalassemia.

So there's two objectives we'll be presenting today. The first is to investigate whether relatively high deferasirox dose and relatively lower body iron burden as measured by serum ferritin, either together or independently, increased the risk for acute kidney injury. The second is to determine whether the exposure-adjusted incidence rates of clinical adverse events are increased when Exjade dose is greater than 25 mg/kg per day, while serum ferritin is concurrently less than 1,000 micrograms per liter.

So first I'll be presenting the pooled analysis of clinical laboratory data. So, overall, we identified 1367 pediatric patients in the pooled clinical studies. We excluded 117 that were either less than two years of age or

didn't have a diagnosis of transfusion-dependent thalassemia, and we excluded an additional 37 patients that didn't have sufficient laboratory data for analysis. This left the 1213 patients that contributed 162 cases of acute kidney injury and 621 matched controls that had normal renal function. So it was a very high-level summary of the study design.

Renal function was assessed monthly in most patients using the estimated glomerular filtration rate, or eGFR. Acute kidney injury cases were defined as an eGFR less than or equal to 90 among patients with normal baseline renal function. Controls were defined as an eGFR greater than or equal to 120, dosage in mg/kg per day, and serum ferritin in micrograms per liter were available throughout follow-up, and the analysis was conducted using conditional logistic regression.

So this slide summarizes the findings for the effect of Exjade dose on a risk for acute kidney injury. First, we found that a 26-percent

increased kidney injury risk was observed per five mg/kg per day increase in Exjade dosage above the typical starting dosage of 20 mg/kg per day. Larger acute kidney injury risk was observed above larger dose thresholds with a 73-percent increased risk above the threshold of an Exjade dose greater than 30.

This slide summarizes the effect of serum ferritin on risk for kidney injury. First, we found that a 25-percent increased acute kidney injury risk was observed per 250 microgram per liter decrease in serum ferritin starting at 1250 microgram per liter. Larger risk was observed below decreasing serum ferritin thresholds with an 85-percent increased risk below the threshold of less than 1,000 microgram per liter.

This slide depicts the combined effects of having both a serum ferritin less than a thousand while Exjade dose is greater than 30. High-dose deferasirox resulted in a 4.47-fold increased risk for a kidney injury in pediatric patients when serum ferritin was less than a

thousand. Even when serum ferritin was greater than a thousand, a 1.67-fold increased risk for kidney injury was observed at high-dose deferasirox, consistent with dose-related nephrotoxicity. Low serum ferritin values less than a thousand observed a 4.08-fold increased risk for kidney injury among patients taking high-dose deferasirox, and the effect of low serum ferritin was also non-significantly elevated among patients not receiving high-dose deferasirox.

This slide shows the effect of age on risk for kidney injury. Overall, you can see that there was a numerically-larger risk observed in younger pediatric patients two to six years versus seven to fifteen years. However, the differential risk by age did not achieve statistical significance.

Finally, here's a summary of cases of acute kidney injury and there disposition. So acute kidney injury cases had a mean 50.2 percent eGFR decrease from baseline compared with a 6.9

percent eGFR decrease in controls. Most kidney injury cases, 95.7 percent, had a documented recovery to an eGFR greater than 100. After the initial episode, deferasirox treatment was discontinued in 11 patients and the dose was decreased in 12 patients. And the among patients who recovered from kidney injury, 62 had a subsequent episode of kidney injury of whom 30 patients had a third episode and 16 patients had four or more episodes of kidney injury during follow-up.

So next Dr. Kate Gelperin is going to present the results of our second objective, too.

DR. GELPERIN: In addition to the analysis of clinical laboratory data just described by Dr. Bird, the study team conducted an analysis of clinical adverse events in pediatric thalassemia patients from the pooled data set who received an Exjade dose greater than 25 ml/kg per day when their serum ferritin was less than a thousand micrograms per liter.

We calculated incident rate ratios

comparing the incidence of adverse events during the first period when simultaneous criteria for high-dose and low serum ferritin were met with the preceding study period for each of the 157 patients who met the simultaneous criteria for dose and serum ferritin at least once.

Clinical adverse events were reported by study site investigators and tabulated using MedDRA codes. Overall, the incidence of adverse events and serious adverse events was generally higher during periods when patients with low serum ferritin received Exjade dose greater than 25 ml/kg per day. The effect was most striking for adverse events coded within the renal and urinary disorder system organ class with a significant six-fold increased risk.

Adverse events of special interests as defined by the sponsor, as well as adverse events necessitating dose interruption, occurred about twice as often during periods when the simultaneous criteria for dose and ferritin were met compared to the previous study periods.

A five-year pediatric registry was conducted by Novartis in fulfillment of the Subpart H post-marketing study commitment issued at the time of approval to obtain additional safety information on deferasirox in young pediatric patients. The final study report was submitted to FDA in 2016, and those data were included in this pooled analysis of clinical studies.

In addition, clinical laboratory data from the five-tear registry were analyzed to evaluate changes in kidney function over time in children who were two to less than six years old at the time of study entry. Serum creatinine was measured monthly in most patients. However, comparison of serum creatinine values with local reference ranges was found not to be a sensitive indicator of kidney injury and many study sites reported reference ranges that may not have been age appropriate.

As you heard from Dr. Khurana today, there are some issues with relying on unadjusted

serum creatinine values to detect kidney injury, especially in pediatric thalassemia patients who may have low muscle mass and chronic glomerular hyperfiltration. For these reasons, serum creatinine values in pediatric thalassemia patients are often abnormally low, even in the presence of kidney injury. To address this issue, we evaluated eGFR values over time in registry patients as calculated with the appropriate Schwartz equations to take body size into account.

Of the 267 pediatric patients enrolled in the five-year registry, 242 patients had pre- and post-baseline eGFR measurements. Of these, 116 patients had a decrease in eGFR of at least 33 percent observed at least once. Twenty-one of these 116 patients, that's 18 percent, had a dose interruption and an additional 15 patients had a dose decrease within 30 days. This analysis showed that acute kidney injury could cause increased deferasirox levels and potential exposure related toxicity commonly in young

children participating in the five-year registry and often was followed by a dose decrease or interruption of therapy.

Acute kidney injury risk was markedly elevated when relatively high deferasirox dose was administered to pediatric patients with relatively low body iron burden measured to serum ferritin. The findings of our analyses support the role of over chelation as a causative factor for acute kidney injury among pediatric patients receiving deferasirox.

The pharmacokinetic data presented today by Dr. Okusanya showed that even relatively small decreases in eGFR are associated with significantly increased deferasirox plasma concentrations. Because deferasirox-induced nephrotoxicity is dose related, increased drug plasma concentrations can exacerbate kidney injury and lead to escalating toxicity.

I would like to acknowledge the study team who worked on the pooled analyses and especially Fang Tian and Scott Swain who were our

data analysts.

DR. WALDRON: In summary, this was a safety review in response to requests from the Committee following the report of the death of an almost three-year-old child who was receiving a dose of Exjade greater than 30 ml/kl per day when her serum ferritin was less than 1,000. We had an antecedent illness with risks for hypovolemia and who subsequently developed acute kidney injury and failure and hepatic failure.

The findings of the safety review team with direct relevance to this case are: There's a risk of renal impairment associated with acute illnesses that have risks for volume depletion, decreased renal function results in increased deferasirox exposure and increased exposure results in decreased renal function with a potential for an exacerbating cycle and possibly hepatic toxicity, and there is a risk of acute liver failure in children receiving deferasirox. The risks of high-deferasirox dose and low serum ferritin was a measure of body iron are additive

for the development of diminished renal function. There is also a risk of life-threatening adverse events when full-dose Exjade is continued at a time when the body iron burden is approaching or within the normal range.

Based on the findings, the agency entered discussions with the sponsor to modify the deferasirox labels with the intention to improve safe use. The label changes are summarized here, followed by the sections of the label where these changes were applied. These label updates include the modifications related to hypovolemia events; the relationship between plasma drug levels and eGFR; the recommendation to use eGFR rather than serum creatinine during drug initiation and monitoring; the risk of life-threatening organ injury when the full deferasirox doses, when full-dose deferasirox for transfusional iron overload are used while the serum ferritin values are approaching the normal range; the use of serum ferritin value of less than 1,000 as a measure of body iron to indicate

a need for reevaluation of dose and/or monitoring regimen and the related added statement to use the minimum effective dose to maintain iron burden in the target range; the interaction between dose, serum ferritin, and the risk of renal impairment; and, finally, the increased risk of auditory impairment when the over-chelation criteria are met.

These are the members of the safety issue team, and that is the end of our presentation.

CHAIR DRACKER: Thank you to all of you for that presentation. We will now proceed with panel discussions. There will not be a vote at the end of these discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific requests of the panel.

Please, again, mention your name and affiliation, please. Thank you.

MEMBER HOEHN: Sarah Hoehn, Advisory

Committee. I had a question for Dr. Bird. When you were talking about the stage 4 kidney injury, I wondered if there was any data on anyone who progressed to needing dialysis or a renal transplant or any evidence about anyone who had permanent kidney injury.

DR. BIRD: We didn't have any of that data in the full data set. We did lose some patients to follow up, but we can't comment on that any further.

MEMBER HAVENS: Is there information on proteinuria? It seems like there's a lot of confusion about how to interpret pediatric creatinine measurements and perhaps a dipstick protein would be easier for people to interpret if proteinuria occurs as a part of this renal injury since it seems to be tubular.

DR. KHURANA: Proteinuria was included as part of the assessment in the NDA. I can't, I would have to defer to Dr. Gelperin if it was included in the data. I would defer to our safety evaluators for their respective analyses

about whether that was a component, proteinuria, urine protein and creatinine.

DR. OKUSANYA: So in the exposure response evaluation for renal injury, proteinuria and/or increase in serum creatinine was also evaluated. It was an and/or evaluation, so I don't think there were a lot of patients that had elevated proteinuria.

DR. KHURANA: I just wanted to make the additional comment that the assessment of proteinuria is also challenging, particularly with this drug, because it's a known tubular toxin. And so distinguishing whether it's tubular in origin versus glomerular would also be a challenge with the information we have available.

MEMBER OSTER: So just two comments. The first one is the death of the three-year-old, there was a mention of her taking multivitamins. And when I look at the labeling and the recommendations, I think there's been tremendous work here and thank you for that, but I didn't

see anything talking about maybe warning people not to give the children multivitamins or to think about the food intake and iron, not that kids love spinach but you never know. And so that's just one comment about the multivitamins that I didn't see.

And the second one is on dehydration. I don't know how mobile these children are, but, if they are running around on a hot sunny day I didn't see anything in the write-up to say that, again, sports and dehydration should be monitored, as well.

DR. WALDRON: You're correct that we did not evaluate multiple vitamins, and we felt that that was outside of the scope of our review. And often those are not considered to be drugs, and so, frequently, they're not even reported as part of a concomitant medication. There are studies in adults that question the value of multiple vitamins, but I'll just leave that alone. Go ahead.

MEMBER OSTER: I just wanted to -- and

that's fine, but, because the reading, it said that just when we get to that normal, you know, normal state that the iron level is so critical, I just, you know, you never know, is the kid taking a Flintstone with iron? And so I just bring it up, even though it hasn't been studied, that might be something worth mentioning.

DR. WALDRON: It might be helpful to keep in mind that these are children who are getting transfused, which represents a very large amount of iron coming into the body every three to, roughly, five week --

MEMBER OSTER: I was thinking about that when I was making the comment, but I just felt, because it looked to me, granted coming from a non-medical background, that little changes can make a big difference. I just felt I wanted to bring it up.

DR. WALDRON: And there are, for the non-transfusiondependent thalassemia children, there are recommendations that there are multiple vitamins, if you choose to use multiple vitamins,

that don't have extra iron, and so that is something that practicing hematologists often recommend to their patients.

And regarding dehydration, you know, we cited the things that are maybe the most obvious and the most easy to ascertain from the adverse event reports, those events of vomiting, diarrhea, and anorexia, but we could not control whether you're in Minnesota or Alabama in June, you know, so we couldn't do that level of analysis.

MEMBER WADE: Kelly Wade. This was really excellent and really wonderful to have this much data. I'm wondering if, over the past maybe two years, if there have been any reports in the FAERS about liver failure or renal failure. Have these cases stopped coming into the FAERS? And then I also wonder in just kind of an aggregate of looking at maybe pharmacy data or any of your data sets do we know if prescribers are limiting the dose that's being prescribed? Like as we associate with these

higher doses, do you have any pharmacy data or anything that says perhaps hematologists are aware of these warnings?

DR. WALDRON: I'll answer the first or the second question first. The label change just occurred in May of this year and so four months ago, and in the end of August Novartis, the sponsor, sent "Dear Healthcare Provider" letters to a large number, I think it was in the neighborhood of 10,000 providers. So they've certainly made a good faith effort to raise the awareness of all of these relevant label changes.

Typically, we would not get that level of data to say that we know the dose in terms of milligrams per kilogram per day that a prescriber would get, so I don't think that we would be able to answer that or whether anyone else wants to make a comment on that.

But your first question of has this stopped, Dr. Crew who is sitting at the table over there was involved in the original FAERS search and then did an update because it had been

two years from the original search. And at that time, there was one additional patient who was an adolescent and had this exact picture of high-dose low-body iron renal failure and hepatic failure. And so, you know, that was prior to the labeling update, of course. We're optimistic, but, you know, sometimes the word gets out and it's practice, sometimes it isn't. So we'll have to wait and see at this point.

MEMBER HOEHN: This is a follow-up to the two other questions. I think it's awesome all the work that's been done in terms of raising awareness and education, but I wondered if there were any specific documents targeted towards the family, like an informed consent or anything they had to sign, because I'm sure a lot of children get viral illnesses and get mild dehydration and they don't necessarily call their pediatrician every single time. So I didn't know if there were any specific family documents that were created to go to the families or any specific consent for families so they acknowledge that

they're aware of the risks of dehydration.

DR. WALDRON: Of course, consent is at a practitioner level and it's not something that the agency has any influence over. And I will ask the Deputy Director for Safety, Barry Miller, as far as I recall, there was no modification of the med guide. That was my recollection. Could you confirm? And I think that's responsive to your question.

CHAIR DRACKER: Use the microphone, please. Just identify yourself, please.

MR. MILLER: Barry Miller from the Division of Hematology Products. Exjade, you're right, does not have a medication guide. That would be the sort of setting, that would be the sort of information for a patient's family members. There is, in Section 17 of the label there is a guidance for the prescriber to educate the parents, and that's where the information would be in there. I mean, that is something we considered discussing with the sponsor.

CHAIR DRACKER: Thank you. Do you

have another question? No? Okay. Anyone else? Okay. We will take a 15-minute break, and then we'll resume and have two informational sessions. Thank you.

(Whereupon, the above-entitled matter went off the record at 2:32 p.m. and resumed at 2:57 p.m.)

DR. DRACKER: And we have two FDA presentations, which are informational only. There will be no discussions. The first is an update on the safety of long-acting beta agonist or LABAs, which I love that acronym.

Thank you. All right.

DR. LIM: So, good afternoon. My name is Robert Lim. I am a pediatric pulmonologist and a clinical team leader in the Division of Pulmonary, Allergy, Rheumatology Products. And in my presentation today I'll just be giving an update on the safety of long--acting beta agonists and asthma.

Here is an outline of my presentation. I'll first begin with some background on the

LABA safety issue, followed by a discussion on the LABA safety trials, as well as well as their individual results, as well the results of the FDA meta-analysis of those LABA safety trials. And, this will be followed by the effect that these have had on the labeling. And then, a summary of my presentation.

So, as of most of you know, there's been a longstanding ---- there have been longstanding LABA safety concerns regarding increased risk of serious asthma outcomes, such as asthma related hospitalizations, intubations, and deaths. And these concerns initially stemmed from the results of the Serevent Nationwide Surveillance study or SNS.

And we're again raising the Salmeterol Multicenter Asthma Research Trial or SMART. Due to these safety concerns, the FDA also performed a meta-analysis back then, which raised similar concerns and also showed a potential increase risk of hospitalization in pediatric patients.

Due to these concerns there is an

extensive regulatory history, with multiple advisory committee meetings, labeling change ---- and the labeling changes, which ultimately resulted in a box warning for all LABA containing products.

The FDA also required large post-marketing in safety trials to evaluate the risk of LABA when added to ICS. And these trials are complete.

This slide summarizes the results of via FDA's previous meta-analysis, which led to the pediatrics safety concern regarding asthma related risks in that population. And, based on that meta-analysis that was previously done, there appeared to be a trend for increased risk for serious asthma outcomes with the decreasing age.

The next couple of slides will summarize a relevant regulatory history. I'll start with some important milestones, starting back in the 90's and then spanning through early 2005.

The green boxes show the LABA products approved for asthma around this time. The first LABA approved for -- was salmeterol inhalation aerosol in 1994. Then, around 2001 -- 2000, 2001, the first ICS/LABA combination product was approved, as well as the first formoterol product.

The blue arrows represent the large safety studies with salmeterol as stated in the previous slide. Data from these studies showed an increased risk in serious asthma outcomes with the use of LABA.

SMART also showed potential that African Americans may be at increased risk. The result of these trials led to a box warning on salmeterol and an advisory committee meeting in 2005 to discuss those results.

This brings us from 2005 to the present. During this period of time, there were multiple new ICS/LABA combinations approved shown here in these green boxes. There are also multiple advisory committee meetings and

regulatory activities stemming from the LABA safety concerns.

Following the 2005 Pulmonary Allergy Drug Advisory Committee, box warnings and medguides were required on all LABA containing products, the results of SMART were also included in product labeling.

Following the 2008 advisory committee meeting, FDA required further safety labeling changes in -- as well as a risk evaluation mitigation strategy and required post-marketing clinical trials, which I'll be -- we've all just referred to as the LABA safety trials.

The design of these trials was discussed at the 2010 PADAC meeting. And the blue arrow represents the LABA safety trials with the final reports submissions staggered between 2016 and 2017.

The review of which ultimately led to further product labeling changes, including the removal of the box warnings for the ICS/LABA products indicated to treat asthma. In the next

slides, I'll discuss the required LABA safety trials.

So, as you're aware, FDA required each sponsor of a LABA containing product approved for asthma to conduct a large safety trial. These trials were ---- these large trials were important to the FDA, as well as the community. And the design of these trials were discussed in an AC meeting in 2010. And the protocols were finalized in 2011.

The objective was to evaluate the safety of LABA when added to ICS. And the outcome of interest was serious asthma outcomes defined as asthma related hospitalizations, intubations, and deaths. Given the rarity of asthma death, at the time of the design, we anticipated that the results would be driven by hospitalizations.

These trials are ---- also included efficacy set ---- efficacy assessments, which were primarily exacerbation. We had particular interest in including patients less than 18 years

of age in these trials given the previously alluded to pediatrics safety concerns.

These required studies were all similar in design to allow for pooled safety analyses for rare events such as asthma related deaths and intubation. And, to that end, the sponsors worked together on study conduct and shared a joint oversight steering committee and a joint data monitoring committee. Asthma relatedness was also adjudicated by a shared committee.

This slide summarized the required studies in adolescents and adults. There were four concurrent studies, 26 weeks in length, with each of those products listed here.

Each trial enrolled around 11,700 patients aged 12 years and older with asthma. At least ten percent of patients were required to be 12 to 17 years of age so that we would get data on that population.

And the treatment groups were ICS/LABA versus ICS. The primary in point was serious

asthma outcomes defined as asthma related hospitalizations, intubations, and deaths.

These trials were all non-inferiority in design. And, each trial was individually powered to have 90 percent power to rule out a two fold increase in event rate.

Given the specific concerns regarding pediatrics safety, a separate LABA safety study in patients 4 to 11 years of age was required. This study was for Advair as this was the only ICS/LABA product approved for this age group.

The design was overall similar to adults with the following notable differences. First, the trial was smaller. It only included 6,200 patients and obviously the patient population was different with the patients being 4 to 11 years of age. Additionally, this ---- because of the smaller size, this provided power ---- this provided 90 percent power to rule out a 2.7 fold increase in event rate.

In all LABA safety trials, efficacy was also evaluated in terms of exacerbations,

where each exacerbation was defined as deterioration asthma requiring the use of systemic corticosteroids, in-patient hospitalizations, or an emergency department visit requiring systemic steroids.

The trials were completed in a staggered manner and submitted to the FDA The approximate dates for their completion are shown here in this slide. It's worth noting that Novartis withdrew from formoterol fumarate from the U.S. market and so terminated their LABA safety study.

Overall, each completed trial excluded the prespecified noninferiority margin and there were very few events of intubations and deaths across all trials. There were also significant decreases in protocol defined as asthma exacerbations, which were primarily driven by events requiring systemic steroids.

The numerical results for the safety analysis are summarized in this slide. Across the top are the individual trials and the columns

are the results for serious asthma outcomes overall, and then broken down by their individual components.

First, I'd like to draw your attention to the results from the adolescent and adult trials, boxed in red. As you can see, the hazard ratios were around 1 with 95 percent confidence intervals excluding the prespecified noninferiority margin of 2.

Results for the pediatrics Advair study also demonstrated a hazard ratio of around 1 with 95 percent confidence intervals, excluding the prespecified margin of 2.7. As previously noted however, there were very few deaths or intubations and the outcome was driven primarily by asthma related hospitalizations.

A meta-analysis was also performed using the adult adolescent data. The results of the meta-analysis are summarized in this table. And, consistent with the individual studies, the hazard ratio for the meta-analysis is right around 1 with an upper limit of the 95 percent

confidence intervals of 1.44.

Overall, the data from the individual studies and meta-analysis did not show significant increase in risk of serious asthma related events with ICS/LABA fixed dosage combination compared to ICS alone. Though these trials were not designed to rule out all risk for serious asthma related events.

As we had the pediatric safety concern, this slide summarizes these subgroups -- -- summarizes subgroup analysis by age, broken down by 12 to 17, 18 to 64, and greater than 64. And these results are consistent for each age group with the primary analysis and do not suggest an increased risk with decreasing age.

In this slide, I've just shown the basically the same graphically. For each of the adolescent adult trials and then the meta-analysis of the adolescent adult trials and then the lowest row is the Advair pediatric trial.

With regard to efficacy, in the

adolescent adult studies, a statistically significant reduction in asthma exacerbations were observed for ICS/LABA versus ICS alone. And, in the pediatrics study, a similar trend was observed, just missed things, statistical significance.

So, as a result of these data analyses, the FDA openly removed the box warning from the ICS/LABA products. The warnings were also revised to emphasize the risk of LABA monotherapy and to describe the results from these trials and the meta-analyses.

As the box warning was removed, the medguide was also changed to a patient information leaflet and although these trials were ---. And although when these trials were initially required, as like excuse me---.

Although we had initially planned to take this to AC when these trials required, the FDA, given the nature of the results, how they were relatively clean across all studies, and in the interest of expediency, this action was taken

without an advisory committee meeting.

So, this action effected the labeling of six products including those products, which were not included in the LABA safety trials. These products are listed in this table.

The grayed out rows are for those products which did not conduct their own LABA safety study. For the single ingredient LABA products listed here, the labeling on the box warning are entirely unaffected.

And so, in summary the required LABA safety studies all met the prespecified non-inferiority margins in the FDA combined analysis. Not surprisingly, the findings were similar. And additionally, sub-group analyses across multiple sub-groups were consistent with the overall analyses.

ICS/LABA treatment also resulted in decreased exacerbations compared to ICS alone for the studied products. And given these data, the box warning was removed from the ICS/LABA contained products, which were indicated to treat

asthma. Thank you.

DR. DRACKER: Okay, thank you very much for the presentation. Next we have a discussion on gadolinium.

DR. FOTENOS: Good afternoon and welcome to the end of your long meeting day. My name is Anthony Fotenos and I'm a Medical Officer in the Division of Medical Imaging Products.

I have been asked to provide an update on the agency's approach to the safety issue of gadolinium retention after administration of gadolinium based contrast agents. Let's see if this ----

By way of introduction, here are a few key facts about the gadolinium based contrast agents or GBCAs. They are the only approved class of drugs for use when MRI ---- for use with MRI in the United States. They are the most intravenously administered drug class after saline iodinated contrast agents.

They are mainly indicated to detect and visualize areas with disrupted blood brain

barrier and/or abnormal vascularity of the central nervous system based on efficacy evidence that blinded readers report improved visualization ratings when comparing pre-plus post-GBCA images to pre-GBCA images alone.

And FDA recognizes that off-label use is common for general anatomical and certain functional diagnostic information provided by MRI across body regions.

The next slide provides a summary of the seven GBCAs currently marketed in the United States. The take home from this busy table is the communication involving GBCAs is clearest using trade names.

Magnevist, the first GBCA was approved in 1988 and approval for the foremost recently marketed agent starting with MultiHance extends down to term birth. So that's the introduction to the GBCA drug class.

Now, let's talk about the classified safety issue. A good starting point for the gadolinium retention story is 1984 with the

publication of the first paper on a GBCA, excerpts of which are shown on this slide.

Starting in the upper left with the chemical structures, the paper described how atoms of gadolinium, an element from the lanthanide row of the periodic table, could be combined with an organic DTPA chelate to create the gadolinium DTPA complex, later renamed ---- later named Magnevist, shown in slide center.

The innovation here was that the complex still interacted with local water molecules to add contrast to MRI images. But, with less toxicity compared to after injection of gadolinium alone as shown by the 20x decrease in rat LD50 values highlighted in the table on the upper right.

Turning to the tables on the bottom, also notable was that mass balance excretion of the drug from rats increased from a couple of percent points after injection of simple gadolinium highlighted on the left, to excretion of 97 percent range after injection of chelated

gadolinium highlighted on the right.

The latter small gap between almost 100 percent excretion and 100 percent excretion, which was easy to minimize by comparison to simple gadolinium is the recurring theme of the gadolinium retention story.

So let's fast forward 15 years. By 1999, Magnevist and two other GBCAs were widely marketed having received U.S. and international approval based on studies demonstrating favorable benefit-risk.

Indeed, the class was generally believed to be safer compared to iodinated contrast agents for X-ray imaging as illustrated by this particularly colorful quote from a publication by a leading GBCA chemist.

The successful penetration of gadolinium chelates can be measured in many ways. The inert complex actually does not look like much at all. A little hydrophilic ball, as innocuous as a sugar molecule and oddly enough it appears to be as safe.

That same year, Shawn Cowper and his colleagues published their first case series on a mysterious new disease they called scleromyxedema-like cutaneous diseases in renal dialysis patients. Not until seven years later would this new disease be linked to GBCAs and renamed nephrogenic system fibrosis or NSF.

In 2006, NSF was discovered to be a serious delayed systemic and chronic rare adverse Fibrosine reaction to GBCA administration. It was observed only in patients with renal failure.

Unfortunately, incident cases have declined toward near zero since GBCAs were contraindicated or relatively contraindicated as detailed in these current classified black box warnings finalized in 2010.

I wish I could report that our story drew to a tidy conclusion here almost a decade ago. But, it didn't. In 2014, a paper was published out of Japan linking a subtle MR Imaging finding of increased signal intensity in the globus pallidus indented nucleus.

The latter shown here to prior GBCA administration even in patients with normal renal function. Follow up animal and autopsy studies have confirmed that this imaging finding is indeed caused by brain gadolinium retention.

The discovery that nanomole per gram concentrations of gadolinium remain in the brain after GBCA administrations surprised everyone for at least two reasons. First, GBCAs were understood not to cross the intact blood brain barrier.

And second, to the extent gadolinium was retained anywhere in the body of patients with normal renal function, the levels were generally considered to be undetectable outside of all but the most sophisticated chemistry labs.

So, how have we responded to this surprise? Our focus has been on guiding rapidly growing research into gadolinium retention toward one main question. What are the safety implications?

In July 2015, we issued the first of

three drug safety communications to address this question stating that recent publications have reported to positive GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans. And that it's unknown whether this is harmful.

Last May, after European authorities announced that marketing authorization might be withdrawn for certain GBCAs, we provided an update to the effect that all GBCAs are associated with the retention in the brain and other body tissues, but that no available evidence suggested this was harmful. Restricting GBCA use was not warranted.

Finally, last September we convened an advisory committee to address public concern around the safety issue culminating in the announcement that sensitive safety studies have potential to build on mostly reassuring evidence reviewed to date and that a new class warning and medication guide, human and animal studies, and enhanced pharmacovigilance were required going

forward.

The next slide summarizes the key messages of the new label warning for clinicians and medication guide for patients. MRI with a GBCA helps your doctor to see problems better than an MRI without a GBCA.

GBCAs contain a metal called gadolinium. Small amounts can stay in your body including the brain, bone, skin, and other parts of your body for a long time, several months to years.

It is not known how gadolinium may affect you, but, so far, studies have not found harmful effects in patients with normal kidneys. Rarely, patients have reported pains, tiredness and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.

Gadolinium stays in the body more after Omniscan or Optimark than after either Eovist, Magnevist, or MultiHance. Gadolinium stays in the body the least after Dotarem,

Gadavist, or ProHance.

People who get many doses, women who are pregnant, and young children may be at increased risk. Consider retention characteristics when choosing GBCAs for these patients. Minimize repetitive and closely spaced administrations.

I'd like to conclude by shifting from a historical perspective to a preview of our approach to safety evidence generation going forward. Suffice it here to say that we think of the sources of evidence to inform our understanding as falling into descriptive and analytical categories. And that our focus going forward is on the bottom two rows.

On the generation of perspective controlled trials primarily designed to exclude a clinically meaningful magnitude of neural behavioral harm, both in juvenile animal studies and matched control cohort trials in neurologically normal adults. The protocols for which are under active development.

Finally, given the interest of this committee, I'd like to conclude with a slide that focuses on trends in pediatric GBCA use. This figure was prepared by my colleague, Patty Greene from our Office of Surveillance in Epidemiology.

It shows GBCA sales from manufacturers to a sample of pediatric hospitals and clinics and requires a bit more back story regarding the difference between the red macrocyclic and blue linear lines.

Recall from the beginning of our retention story timeline that GBCAs are manufactured by combining gadolinium ions with organic chelating molecules to promote excretion and safety.

Also recall, that there are two black box warnings for NSF with slightly different wording such that MRIs contraindicated for patients with renal failure only for the three agents most strongly associated with NSF.

The geometry of the organic chelate for these three agents, Magnevist, Omniscan, and

Optimark is more open chain or linear compared to the structure of the chelate for ProHance, Gadavist, and Dotarem, referred to as the closed chain or macrocyclic GBCAs.

In particular, compared to the macrocyclics, these three linear GBCAs are both more closely associated with NSF in patients with renal failure and most retained in all patients, including patients with normal renal function.

This figure suggests a clear shift in pediatric use from linear to macrocyclic agents shortly following a period of time when two new macrocyclic agents were approved including supplemental approval down to term birth starting in 2014.

In conclusion, available evidence suggests benefit risk remains favorable for all GBCAs. However, the stronger association of some agents with NSF and theoretical concerns based on relative retention and biochemical properties may represent factors that stakeholders choose to focus on when selecting agents from among the

choices on the market. Particularly for populations more vulnerable to subtle and/or delayed harm that is challenging to study, such as pediatric patients. Thank you.

DR. DRACKER: Thank you very much for that presentation.

MS. BRILL: Okay, transportation going back to the hotel, the shuttle will be out in front of Building 1 at ten minutes before 4:00 o'clock this afternoon.

The shuttle can only accommodate, I believe 10 or 12 people so you have an option of calling an Uber. So, you can Uber back to the hotel.

Tomorrow morning at 7:30 a.m., the shuttle will pick you up and then drop you off here. So, it's 7:30. Please try to wait for your colleagues.

Again, space is limited so you may Uber coming to the FDA And, if you haven't not turned in your CDCF, please leave them on your desk or a on the tables and then we will collect

them. Thank you.

Oh, we will have a training tomorrow that's going to start at 8:30 a.m. So, they will go over some labeling regulation and a whole stuff. Suzie, you want to say something more about it?

DR. MCCUNE: This is just an opportunity for us to go over some aspects of FDA 101 that we've heard today a little bit. We're going to talk about drug regulations and drug approval processes, efficacy safety, and then drug labeling.

So it should be a --- and very relevant to the conversations that we have had --- you've had today and that the presentations that we've heard.

DR. DRACKER: I want to thank everyone. I think you've helped the FDA quite a bit. And I think we appreciate all the hard work that the FDA does as well. So, thank you Suzie. Thank all of you.

(Whereupon, the above-entitled matter

went off the record at 3:22 p.m.)