

## 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

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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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## CONTENTS

Introductory Remarks	
Dr. Bob Dracker.....	5
Conflict of Interest Statement	
Ms. Marieann Brill.....	6
Opening Remarks	
Dr. Susan McCune.....	14
Office of Pediatric Therapeutics Updates	
Dr. Judith Cope.....	24
Open Public Hearing .....	27
FDA CDER Standard Review of Adverse Event Presentations:	
Lexapro (escitalopram oxalate)	
Dr. Courtney Suggs.....	35
Generic Drugs Topic: Drug-Ineffective Postmarketing Reports in Drug Safety Evaluation	
Dr. Cindy Kortepeter.....	50
Generic Drug Development and Safety Evaluation	
Dr. Howard Chazin.....	64
Ituniv (guanfacine ER)	
Dr. Amy Taylor.....	164
Summary of FDA Completed Review of Pediatric Safety Issues and Updated Labeling Changes for Exjade (deferasirox)	
Dr. Peter Waldron .....	204
Discussion	
Drs. Olanrewaju Okusanya, Mona Khurana, Steve Bird, and Kate Gelprin.....	215

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CONTENTS

Update on the Safety of Long Acting Beta Agonists  
(LABA)  
    Dr. Robert Lim..... 252

Update on FDA Approach to Safety Issues of  
Gadolinium Retention after Administration of  
Gadolinium-Based Contrast Agents  
    Dr. Anthony Fotenos..... 265

Adjourn ..... 277

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
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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

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

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

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

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

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

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

3                   MS. BRILL:       Good morning.       The  
4 following announcement addresses the issues of  
5 conflict of interest with regards to today's  
6 discussion of reports by the Agency as mandated  
7 by the Best Pharmaceuticals for Children Act and  
8 the Pediatric Research Equity Act.

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

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

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

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

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

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

22 Those interests may include



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

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

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

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

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

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

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

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

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

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

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

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

22 MEMBER SAYEJ: Wael Sayej, pediatric

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

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

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

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

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

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

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

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

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

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

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

22                   MEMBER HOEHN: Sarah Hoehn. I am

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

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

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

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

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

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

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

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

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

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

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

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

22 MS. MCCUNE: Good morning all. Thank

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

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

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

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

22 She received her medical degree from

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

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

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

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1 Liverpool, New York.

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

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

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

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

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1       hypothermia, aspiration, and anesthetic toxicity.

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

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

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

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1 2012 and brings immense knowledge of the  
2 healthcare system.

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

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

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

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

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

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

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

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

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

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

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

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

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1           We had a number of talks about current  
2 approaches to pharmacovigilance followed by  
3 future directions involving large databases,  
4 electronic health records, and even social media.

5           We will be discussing internally how we might  
6 augment the pediatric safety information that we  
7 bring to the PAC in the future.

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

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

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

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

4 CHAIR DRACKER: Thank you, Dr. McCune.

5 We will now have Dr. Judith Cope, Safety Team  
6 Leader, provide updates for the Office of  
7 Pediatric Therapeutics.

8 DR. COPE: So good morning, and  
9 welcome, and thanks for everybody in attendance.

10 And we look forward to your participation in our  
11 meeting today.

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

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

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1 are different for the pediatric age group  
2 approval.

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

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

16 So there was a label change that  
17 happened the following year, in December of 2016.

18 And important information on the neuropsych  
19 events was put into the warnings and precautions,  
20 the adverse reaction section, and also in the  
21 part of the label that is the patient counseling  
22 information on how parents should handle stuff

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1 and definitely contacting their healthcare  
2 provider.

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

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

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

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

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

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

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

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

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

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

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

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

22 For this reason, the FDA encourages

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

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

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

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

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

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

10 Will Speaker Number 1 please stand up?

11 DR. SRINIVASAN: Good morning.

12 CHAIR DRACKER: Thank you.

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

22 We do not accept funding from drug and

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

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

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

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

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

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

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

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

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

22 Although the number of these adverse

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

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

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

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

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

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1 acknowledge you so we can do so.

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

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

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

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

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

6 We will now proceed with the FDA  
7 presentation.

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

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

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

22 Escitalopram or Lexapro was originally

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

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

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

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

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

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

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

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

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

3 One hundred and sixty-five patients  
4 were enrolled, and the population consisted of  
5 108 --- the safety population included 118  
6 patients consisting of all patients enrolled in  
7 the study who took at least one dose of  
8 escitalopram.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1                   Section       12       describes       the  
2       pharmacokinetics in adolescents. In a single-  
3       dose study of escitalopram, 10 milligrams, the  
4       AUC decreased by 19%, and the Cmax increased by  
5       26 percent in healthy adolescents compared to  
6       adults.

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

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

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

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

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

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

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

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1 period ending March of 2017.

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

9 So for our review, we reviewed 645  
10 pediatric reports with a serious outcome. Of  
11 these, 74 reported the outcome of death. We  
12 excluded 633 cases, including the 74 deaths. The  
13 463 transplacental or breast feeding patients  
14 were reviewed but excluded.

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

22 According to the CDC, birth defects

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

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

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

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

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

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

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

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

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1 next two weeks up to and including suicidal  
2 ideation.

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

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

12 There was a 15-year old who refilled  
13 escitalopram with a new generic version and  
14 developed anxiety and behavioral dysregulation  
15 similar to what she exhibited prior to treatment.

16 And her symptoms improved significantly with  
17 brand Lexapro. And this was the only case out of  
18 the five that included any tablet identifying  
19 information.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 Dr. Kortepeter?

22 DR. KORTEPETER: Good morning. My

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

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

10 We recently completed a study on  
11 reports of drug ineffective, reports from FAERS.

12 So we thought that this will be a good  
13 opportunity for us to give an overview on our  
14 experience with Drug Ineffective Post-marketing  
15 Reports and drug safety surveillance. I will be  
16 using the terms lack of effect and drug  
17 ineffective synonymously throughout this  
18 presentation.

19 Here's an outline of the presentation.

20 I will begin by providing background information  
21 on spontaneous adverse event reports and the FDA  
22 Adverse Events Reporting System database, as well

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1 as background on reports of drug ineffective in  
2 the database.

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

7 Most of you are probably familiar with  
8 this slide on how safety reports get to the FDA.

9 Our spontaneous Adverse Event Reporting System  
10 is set up so that anyone can report a suspected  
11 adverse event.

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

22 Regardless of how FDA receives these

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

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

10 Currently, there are more than 14  
11 million reports in the system with the earliest  
12 reports dating back to 1968. Last year alone, in  
13 2017, more than 1.8 million reports were entered  
14 into the database.

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

22 The manufacturers are required to

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

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

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

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

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1           ineffective as a reportable adverse event.

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

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

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

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

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

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

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

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

22 In other words, a report was



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

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

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

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

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1 review of 552 reports and determined that 43 of  
2 the 552 were deemed useful. The sample size of  
3 552 were calculated by our statistician who took  
4 into account a prevalence rate as well as the  
5 precision of drug ineffective reports with  
6 potential utility.

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

12 This slide compares the approximately  
13 250,000 drug ineffective reports to the 3.6  
14 million non-drug ineffective reports during the  
15 study period.

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

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1 equal numbers of consumers versus healthcare  
2 professionals.

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

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

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

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

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

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

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

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

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

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

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

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

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1 study period.

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

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

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

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

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

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

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

22          I'd like to acknowledge my colleagues

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

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

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

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

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

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1 some basic information in order to frame the  
2 presentation.

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

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

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

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

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1 drug approvals reaches back to the Drug Price  
2 Competition and Patent Term Restoration Act of  
3 1984, also known more commonly as the Hatch-  
4 Waxman Amendments to the Food and Drug and  
5 Cosmetic Act.

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 those products that are on the market.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 These studies establish reliable

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

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

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

15 These measurements are surrogates for  
16 rate and extent of absorption of the product.  
17 However, to demonstrate bio-equivalence, the  
18 statistical analysis must show the ratios of  
19 generic to the brand of these parameters must  
20 remain within a 90 percent confidence interval of  
21 0.8 to 1.25.

22 If that gets a little bit beyond your

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22           So luckily, there is a regulation that

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

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

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

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

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1 equivalence and clinical reviewers.

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

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

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

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

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

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

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

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

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

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1 removed from the market due to potential safety  
2 concerns.

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

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

17 We primarily use an internal database  
18 at FDA called the Drug Quality Reporting System.

19 This is a subset of MedWatch reports that mostly  
20 contain complaints related to quality or  
21 inequivalence of drugs. These drug quality  
22 reports may also contain adverse event

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

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

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

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

22 Sometimes, this slide is old, but

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 In fact, the safety reviewer has to

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

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

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

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

7           The monthly committee, if it can't  
8 make a decision, then brings its safety concerns  
9 to the larger bi-monthly OGD Safety and  
10 Surveillance Committee meeting which has  
11 representation from all of CEDR's super offices.

12         The bi-monthly committee helps to make a final  
13 decision on the controversial or emerging issues.

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

19           CHAIR DRACKER: Thank you, Dr. Chazin.

20         We will - I just want to mention that the public  
21 hearing period is now closed. It closed at  
22 10:16. We will now proceed with questions to the

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1 committee and panel discussions.

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

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

13 MEMBER SAYEJ: Thank you, Dr. Dracker.

14 This is Dr. Wael Sayej from Connecticut. I just  
15 have a couple of questions, one with regards to  
16 the drug ineffectiveness reports. Do we have any  
17 idea if there's any reporting of the length of  
18 time that these patients were on the drug before  
19 it was deemed or before it was labeled as  
20 ineffective for them?

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

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

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

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

19 CHAIR DRACKER: Sarah?

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

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

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

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

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

3 MEMBER HOEHN: I just didn't know if  
4 there seems to be a higher rate in the seven to  
5 11-year-olds, if something could be added about  
6 it being contraindicated or other markers because  
7 clearly the rates of suicide in a seven-year-old  
8 are much lower than the rates of suicide in a 15-  
9 year-old.

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

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

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

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

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

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

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

5 CHAIR DRACKER: Dr. McCune?

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

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

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

22 MEMBER McGOUGH: I could just - Jim

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

5 CDR SUGGS: The drug use data?

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

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

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

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

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

9 So I think a single incident or even a  
10 very small incident probably overstates the risk.

11 Practitioners take the burden, and I think  
12 honestly, a lot of doctors overprescribe these  
13 drugs, especially in these younger kids, but  
14 that's kind of their call.

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

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

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

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

12 CHAIR DRACKER: Did you want to  
13 comment?

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

18 CHAIR DRACKER: Speak into the  
19 microphone, please.

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

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

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

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

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

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

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

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1 CDR SUGGS: Yes.

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

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

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

22 CHAIR DRACKER: Any other questions or

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1       comments?

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

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

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

18                  So then when we look at the number of  
19      results that have been reported, we see over  
20      almost four million, and then we looked at  
21      247,000 were coded as drug ineffective, and then  
22      there were 43 events that you actually looked at,

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

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

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

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

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

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

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

8 The other one, it is not clear on the  
9 labeling that we don't know the long-term effects  
10 of this drug, so the studies are done for up to  
11 24 weeks, but how long are these children taking  
12 the drugs? And so therefore, as we look at these  
13 drugs, I think in the, with the data we have, we  
14 have to make a decision to see does this help  
15 families choose a course of action?

16 CHAIR DRACKER: Are there any  
17 comments?

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

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

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

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

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

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1           And we are looking in other ways to  
2           try and get some additional information on drugs  
3           when we do know that there is an adverse effect.

4           Some of the drugs that we're talking about in  
5           the psychiatry realm have effects, say, on weight  
6           gain and growth, and we are doing other studies  
7           to try and take a look at sort of those effects  
8           separately.

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

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

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1 take a look at these.

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

12 But the issue of trying to sort out  
13 the meaning of a report that comes to us about a  
14 drug being ineffective is really difficult when  
15 you think about it within the setting of the  
16 clinical trials. We have all sorts of patients  
17 that are reporting that the drug is ineffective.

18 It's not like the drug is expected to be  
19 effective in everybody in whom it's used.

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

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

6 MEMBER OSTER: Yes.

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

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

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

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1 considering using concomitant use of CNS  
2 depressants and alcohol.

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

8 MEMBER OSTER: Yes.

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

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

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

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

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

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

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

22 DR. LEVIN: Postmarketing data

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1 specifically?

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

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

11 MEMBER HAVENS: Yeah, no -

12 DR. LEVIN: - point of all.

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

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

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

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

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

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

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

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1 DR. LEVIN: Yes.

2 MEMBER HAVENS: - into those age  
3 groups?

4 DR. LEVIN: Yes, we can.

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

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

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

20 MEMBER HAVENS: No, I understand.

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

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

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

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

19 CHAIR DRACKER: Susan?

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

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

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

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

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

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

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

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

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

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1 both onset of efficacy and full efficacy.

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

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

13 MEMBER HAVENS: Thank you.

14 CHAIR DRACKER: Dr. Turer?

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

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

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

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

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

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

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1 data.

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

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

10 DR. LEVIN: Oh, yeah, well, that's the  
11 longest half-life drug, yes, about four to six  
12 weeks of the active metabolite, but still 24 to  
13 32 is a very long half-life compared to most  
14 products, so I think that alone, for that point,  
15 we wouldn't necessarily have concern about PK  
16 effects or PK/PD.

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

22 MEMBER TURER: Correct.

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1 PARTICIPANT: - referring to?

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

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

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

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

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

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

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

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

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

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

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

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



1 MEMBER PORTMAN: Can I comment on  
2 that?

3 CHAIR DRACKER: Dr. Portman, was that  
4 you?

5 MEMBER PORTMAN: Yes, it was.

6 CHAIR DRACKER: Did you have a  
7 question?

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

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

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

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1 be clear. Thank you.

2 CHAIR DRACKER: Go ahead.

3 MEMBER PORTMAN: Thank you.

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

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

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

21 CHAIR DRACKER: Yes?

22 DR. HAUSMAN: Hi, Ethan Hausman.

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

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

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

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

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

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

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

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

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

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

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

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

22 There may be some really rare bio INDs

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

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

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

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

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

7 MEMBER JONES: Okay, thank you.

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

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

22 So probably to address several

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22           And if we do see that this is actually

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

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

8 DR. CHAN: We do, definitely.

9 MEMBER JONES: Okay.

10 CHAIR DRACKER: Okay, Dr. Flick?

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

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

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

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

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

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

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

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

15 CHAIR DRACKER: Okay, Dr. Wade?

16 MEMBER WADE: Thank you.

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

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

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

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

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

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

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1 MEMBER FLICK: - which we know is -

2 DR. LEVIN: - are very much in flux.

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

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

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

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

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1 a particular type of adverse event?

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

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

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

22 If the event is a high background

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

8 We can really never confirm, but we  
9 often do make decisions based on FAERS' reports.

10 But I guess the answer is yes to your question.

11 If we had some type of qualitative severe event  
12 that we thought was unusual, we could and would  
13 pursue that in various ways.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 CHAIR DRACKER: Dr. Sayej?

18 MEMBER SAYEJ: Thank you, Wael Sayej.

19 I have a quick follow-up question to Dr. Jones'  
20 questions and I just want to make sure I  
21 understood this properly and I have a couple of  
22 comments after that.

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

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

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

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

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

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

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

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

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1 studies when they're available.

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

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

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

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

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

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

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

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

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

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

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

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

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

17               CHAIR DRACKER:    Sure.

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

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

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

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

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

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

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

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

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

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

22 But of course we're dealing with

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

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

12 As far as some mentioned here about  
13 whether this is a question of pushing someone  
14 over the edge, that doesn't seem to be the case.

15 It really looks more like when suicidal,  
16 treatment of emerging suicidal behavior that's  
17 drug related is an independent effect that has,  
18 that's unrelated to the underlying depression or  
19 much less related to the underlying depression  
20 and particularly in younger people.

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

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

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

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

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

22 DR. STONE: I'm the Deputy Director

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1 for Safety in the Division of Psychiatry  
2 Products.

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

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

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

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

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

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

17 I also want to just talk a little bit  
18 about on this medication guide, it says, "What  
19 should I avoid while taking Lexapro?" and we're  
20 talking about people that are under the age of  
21 17, and it says that they shouldn't operate heavy  
22 duty vehicles.

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

6 And then the last point I'd like to  
7 make is when we're looking at, you know, "What do  
8 I do?" the recommendation of "How do I get my -  
9 you know, I've had an event," it does give the  
10 800 number for the FDA for the MedWatch.

11 We've already had very good reporting  
12 here about how few data we're getting from  
13 consumers, and it doesn't have the website, okay?

14 And I did look up you do have a website, and so  
15 I would definitely advise that the website is  
16 added to this and to make sure that it's easy.  
17 Thank you.

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

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

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

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

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

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

5 Please press the button on your  
6 microphone that corresponds to your vote. You  
7 will have approximately 20 seconds to vote.  
8 Please press the button firmly. If you have made  
9 your selection, the light may continue to flash.

10 If you are unsure of your vote or you wish to  
11 change your vote, please press the corresponding  
12 button again before the vote is closed.

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

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

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1 approach to the question?

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

7 MEMBER OSTER: Okay, thank you.

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

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

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

21 (Pause.)

22 MS. BRILL: For the record, the

1 results are 11 yes, zero abstain, one no.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13                   MEMBER ANNE:   Premchand Anne, I voted  
14 yes.

15                   MEMBER CALLAHAN:   David Callahan, I  
16 voted yes.

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

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

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

14          MEMBER HAVENS: Peter Havens, I voted  
15          yes.

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

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1                   (Whereupon, the above-entitled matter  
2 went off the record at 11:39 a.m. and resumed at  
3 11:55 a.m.)

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

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

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

14                   Intuniv or guanfacine extended release  
15 was first approved for marketing on September 2,  
16 2009. It is a central alpha<sub>2a</sub> adrenergic receptor  
17 agonist.

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

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

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

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

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

14 The second review was in September  
15 2013 and it raised a concern for hallucinations  
16 as a safety signal. Hallucination was added as  
17 an adverse event to labeling in 2013.

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

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

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

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

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

12 The second was when information on  
13 maintenance treatment was added on March 18,  
14 2015.

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

21 The number of pediatric patients  
22 receiving guanfacine ER gradually increased from

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

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

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

14 I will now discuss the safety review  
15 of FAERS reports. This table shows the total  
16 adult and pediatric FAERS reports from July 1,  
17 2009 to May 31, 2017 with guanfacine ER.

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

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

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

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

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

17 She died at home from complications of  
18 portal and splenic ~~vainvein~~ thrombosis.

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

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1                   Concomitant medications included  
2 propranolol.

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

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

12                   In the next several slides I will  
13 present the remaining 32 cases of unlabeled  
14 serious adverse events. There were 23 cases with  
15 psychiatric adverse events. Nine of the cases  
16 contained aggression and self-injurious behavior.

17                   Six of the nine cases were confounded by the  
18 patient's medical history. One occurred after a  
19 missed dose of medication. Another after use of  
20 generic guanfacine, and one after an increase of  
21 the guanfacine from 1 to 2mg.

22                   There were seven cases with adverse

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 notice anything new or different from the  
2 labeling.

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

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

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

15 So for example, this is an alpha  
16 agonist, in the same class of drugs as clonidine.

17 Clonidine was actually tested in the seventies  
18 and the eighties because of its known impact on  
19 appetite.

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

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1       guanfacine they get hungry.

2                   The somnolence is absolutely true too.

3       I actually missed that it wasn't on the label.

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

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

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

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

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

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

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

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

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

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

4           MEMBER TURER: But it differs by age.

5           So in any trials that include let's say 2- to  
6 18-year-olds, or 6- to 18-year-olds you're going  
7 to have some adolescents who may not have height  
8 change whereas a 6-year-old is going to be on  
9 their peak height trajectory where it's going to  
10 change quite rapidly.

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

15           DR. STONE: Well, we do have BMI data.

16           That's always calculated. In an adult trial  
17 you're not going to repeatedly measure people's  
18 heights but in a pediatric trial you do.

19           MEMBER TURER: Yes.

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

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

4 MEMBER CALLAHAN: David Callahan,  
5 child neurologist.

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

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

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

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

6           My second comment is the aggression  
7           and the irritability. I'd have to look back, I  
8           don't know if that's in the label or not but I  
9           warn all parents that some kids have the opposite  
10          reaction that we're looking for. We're looking  
11          for improved self-control and clearly some kids  
12          it makes them irritable and angry and aggressive.

13          I see that on a frequent enough basis that I  
14          think it's a real side effect.

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

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

22          MS. CHENG: This is Carmen. So in our

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

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

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

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

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

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

4 CHAIR DRACKER: Dr. Havens.

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

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

11 It seems to suggest -- this is in the  
12 SPD503 study 315 which was for long-term benefit.

13 Is this making sense to anybody? It was sent as  
14 a part of the packet. If we're not supposed to  
15 review it and talk about it then it's okay. But  
16 I just had a question. No?

17 DR. STONE: I wouldn't --

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

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1 argues that it doesn't work long-term.

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

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

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

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

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

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

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

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

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

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

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1           And that half had failed by 56 days,  
2           whereas half had not. So I don't know if that --  
3           it certainly argues for ongoing clinical review.

4           I am supportive of what the FDA has --

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

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

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

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

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

18          MEMBER HAVENS: Okay, thank you.

19          CHAIR DRACKER: Yes.

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

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

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

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

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

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

22 DR. MCCUNE: And just to follow up

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

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

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

14 I think triglycerides, I don't know  
15 how often they are checked but triglycerides over  
16 500, 500 to 1,000 could put the child at risk for  
17 pancreatitis.

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

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1 considering some other medication other than  
2 Intuniv.

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

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

10 MEMBER ANNE: The AAP recommends this  
11 universal screening and everything between 9 and  
12 11 years of age. And then if there's any other  
13 risk factors and so on and so forth. But only  
14 about 15-20 percent -- what is it, about 60  
15 percent know about the guidelines but only 15  
16 percent actually follow this.

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

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

22 MEMBER OSTER: Yes. So, again the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 Thank you.

20 CHAIR DRACKER: Thank you. Yes.

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

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

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

8 And part of that review is -- and if  
9 there are perceived changes in the frequency or  
10 severity they're not excluded, they're included.

11 So even if it is already labeled it's not just  
12 that something is labeled so it's not looked at  
13 and it's not addressed.

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

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

6 Anyone else? Yes.

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

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

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

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

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

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

16 So we don't have any major concerns.  
17 But we are keeping an extra eye on pancreatitis  
18 if we do get good cases that come up.

19 CHAIR DRACKER: And that is one of the  
20 recommendations as well for monitoring.

21 MEMBER ANNE: I think considering  
22 adding the triglyceride level to the label, or

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1       advising the pediatricians to do this I think may  
2       not be a bad idea. You tend to see these things  
3       elevated in the pancreatitis situation.

4               DR. STONE:     I would think you're  
5       adding quite a long chain of connections here.  
6       First, you're assuming the pancreatitis was due  
7       to the drug. Secondly, you're assuming that the  
8       pancreatitis that did occur was due to elevated  
9       triglyceride levels and there are lots of other  
10      reasons for that.

11             So I think we'd have to establish a  
12      little stronger chain of causation before we make  
13      a recommendation like that. We do have data from  
14      clinical trials that do measure triglyceride  
15      levels and there was no marked difference between  
16      drug and placebo otherwise that would be labeled.

17             MEMBER WADE:   Just to follow up on  
18      that I think it would be helpful when this kind  
19      of diagnosis comes up such as pancreatitis if you  
20      could go back into the clinical trials that were  
21      performed that led to the label, if you could  
22      just give us -- I'm sure you've gone back to them

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1 -- to say what we know about pancreatitis from  
2 the original phase 3 trials is that the trials  
3 looked at these specific laboratory tests and  
4 this was the two groups.

5 Because it could be that laboratory  
6 values for pancreatitis were not collected and  
7 therefore we don't have them, or there were  
8 incomplete laboratory assessments on a certain  
9 number of patients.

10 Or it could be that those trials  
11 actually collected really excellent labs related  
12 to pancreatitis and we actually know there was no  
13 difference in the placebo group versus the drug  
14 group.

15 This is kind of an example where I  
16 think going back into that data that you have and  
17 showing us what we actually know from the  
18 randomized controlled trials would be helpful.

19 DR. STONE: I do take your point and  
20 we do measure things like triglycerides. For a  
21 case of pancreatitis, pancreatitis is more of an  
22 all or nothing. It's not quite the same thing as

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1 being a little bit pregnant but if you were to  
2 measure for example amylase levels the fact that  
3 there was a slightly higher amylase level with  
4 drug rather than placebo.

5 First of all, it's unlikely we'd  
6 detect it but even if it were the case it would  
7 probably not be a marker for clinical  
8 pancreatitis. The issue is whether there were  
9 cases of pancreatitis in the clinical trial given  
10 that there are just two reported cases among  
11 hundreds of thousands or millions of people who  
12 have taken these drugs. The incidence is likely  
13 extremely low and not going to show up in a  
14 clinical trial.

15 That's the problem we always face with  
16 trying to evaluate safety initially in a clinical  
17 trial.

18 CHAIR DRACKER: Anyone else? Yes.

19 MEMBER FLICK: So I just want to  
20 reinforce a little bit. So what we have are two  
21 cases out of many, many thousands with no  
22 comparator.

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1           So we really don't have a rate and we  
2           don't have a comparator.     So what is the  
3           frequency of pancreatitis in the population not  
4           taking this medication.     It may be higher, I  
5           don't know.

6           And then the flip side of this is if  
7           we were to ask to have that label changed to ask  
8           for metabolic testing we have to consider the  
9           imposed cost.

10           So now you're going to test literally  
11           tens of thousands of people at a cost that's  
12           extraordinary trying to find a very few cases  
13           that may actually be similar to the frequency  
14           within the population.

15           So the ability to detect a true  
16           positive in that would be extraordinarily low and  
17           the cost would be extraordinarily high to detect  
18           each one of those true positives.

19           So from an epidemiologic standpoint it  
20           doesn't make sense unless you have better data  
21           that would help you'd rive that.

22           Randomized controlled trials or the

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1 kinds of studies that are done for approval are  
2 never large enough to pick up these kinds of  
3 events although you might -- I would maybe differ  
4 with you and say that if you had an elevation of  
5 amylase even slightly above what you see in the  
6 control group that would tend to make you want to  
7 look at this more closely even though you didn't  
8 have pancreatitis.

9 MEMBER SAYEJ: I would just like to  
10 add one more point to what was just said. And I  
11 completely agree with the statement.

12 We can't be digging for one case  
13 amongst millions of patients who are taking it.  
14 These kids who have had pancreatitis most likely  
15 have had triglyceride levels checked when they  
16 were diagnosed with the pancreatitis and it would  
17 be worthwhile to go back and look at those cases  
18 specifically and see if there was any specific  
19 cause for the pancreatitis.

20 Most of the time pancreatitis in  
21 pediatrics is idiopathic. We have no  
22 identifiable cause. Whether it's a viral illness

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1 or medication most of the time there's no  
2 identifiable cause.

3 So I wouldn't rush into trying to  
4 change the label to add the pancreatitis or to  
5 request for any additional testing. I do agree  
6 with continued monitoring and keeping an eye on  
7 this.

8 CHAIR DRACKER: Anyone else. Dr.  
9 Havens, do you have anything else?

10 MEMBER HAVENS: No, but thank you for  
11 asking.

12 CHAIR DRACKER: You're welcome. All  
13 right, are we ready for a vote? And I assume the  
14 medication error involving name confusion is  
15 specific to guaifenesin, correct.

16 MS. CHENG: I'm sorry?

17 CHAIR DRACKER: The medication error  
18 involving name confusion is specific to  
19 guaifenesin?

20 MS. CHENG: Yes. This would be for  
21 Intuniv and Invega that we saw specifically.

22 CHAIR DRACKER: Intuniv and what, I'm

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1       sorry?

2                   MS. CHENG:   Intuniv and Invega.  These  
3       were the cases that we saw.

4                   CHAIR DRACKER:  All right.  Yes.

5                   MEMBER TURER:  Christy Turer.  May I  
6       ask for a clarification.

7                   If we vote routine monitoring can we  
8       separately vote to add something to the label, or  
9       by saying we agree with routine monitoring we're  
10      negating the ability to add something to the  
11      label.

12                  CHAIR DRACKER:    I think that's a  
13      separate issue altogether but I'll let them.

14                  DR. ALEXANDER:  You can still go ahead  
15      and vote yes but make a recommendation if you  
16      want something added.

17                  CHAIR DRACKER:  So you would have an  
18      opportunity to do that after you vote and we go  
19      around the table.  All right.

20                  Shall we take a vote?  I'll read the  
21      question.    FDA recommends continuing routine  
22      ongoing    post-marketing    safety    monitoring

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1 including monitoring for suicidal ideation and  
2 behavior, pancreatitis and medication error  
3 involving name confusion. Does the committee  
4 concur? Please make your vote.

5 Who did not vote. We're okay. Okay,  
6 good.

7 MS. BRILL: Okay, for the record the  
8 results are 11 yes, zero abstain, and 1 no.

9 CHAIR DRACKER: Peter, we're going to  
10 start with you.

11 MEMBER HAVENS: Peter Havens. I voted  
12 yes.

13 MEMBER HOEHN: Sarah Hoehn. I voted  
14 yes. And I do agree to look into the  
15 pancreatitis more to see if there's anything  
16 there.

17 MEMBER MCGOUGH: James McGough. I  
18 voted yes.

19 MEMBER CALLAHAN: David Callahan. I  
20 voted yes. I recommend adding weight gain to the  
21 signals to watch.

22 MEMBER ANNE: Premchand Anne, yes.

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1 MEMBER DICAPUA: Peggy DiCapua, yes.

2 MEMBER CATALETTO: Mary Cataletto,  
3 yes.

4 MEMBER WADE: Kelly Wade, yes.

5 MEMBER OSTER: Randi Oster, no. I  
6 would like to say that the data exists in the  
7 market and I'm hoping that we see the ability for  
8 us to try to get more data so when we have these  
9 discussions we can feel that we have more data  
10 points that we're evaluating.

11 I also would like to say that the  
12 points I made earlier about what I feel should be  
13 on the label regarding the sports should be  
14 added. Thank you.

15 MEMBER TURER: Christy Turer. I voted  
16 yes. I would like weight gain added to the  
17 label.

18 I'd also want to know with the cases  
19 of pancreatitis if they occurred in children with  
20 existing obesity. Because in those children we  
21 are supposed to be checking for lipids a minimum  
22 of every two years and hopefully we'll have

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1 safety systems in place to be able to do that.

2 One I guess question is whether we're  
3 going to be incorporating data from Sentinel, not  
4 just FAERS into these reviews but that can be  
5 dealt with later.

6 MEMBER SAYEJ: I voted yes and I will  
7 make a couple of comments.

8 I think the standard of care is a  
9 little bit different from what the label should  
10 say in many cases.

11 So if we're treating patients with  
12 these medications as pediatricians in general we  
13 should be aware of what the possible side effects  
14 are.

15 Yes, one case out of a million is not  
16 probably going to be labeled but something that  
17 should be part of the general practice in terms  
18 of clinical guidelines. Those are the things  
19 that will guide us in terms of what we test.

20 We had this conversation a couple of  
21 years ago about general guidelines and standard  
22 of care.

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1           The second comment I would like to  
2           make is the one cause of death that we really  
3           never got to talk about it, I certainly agree  
4           with Dr. Dracker about that patient had a lot of  
5           issues going on.

6           Patients with Crohn's disease and  
7           colitis also have a hypercoagulable state and are  
8           more prone to develop portal vein thrombosis,  
9           splenic splenosis just from the inflammatory  
10          process.

11          So there's certainly no evidence of  
12          cause and effect with the medication.

13          MEMBER FLICK: Randall Flick. I voted  
14          yes.

15          CHAIR DRACKER: Okay. We will have a  
16          lunch break. We will reconvene at 1:30.  
17          Marieann needs to say a few things.

18          I just want to remind everyone to  
19          please don't discuss the proceedings we've had  
20          this morning. Thank you.

21          MS. BRILL: A few announcements. For  
22          the panel members the breakout room is in 1404.

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1 I was asked to say that if you ordered and paid  
2 for your lunch your lunch boxes should be in  
3 1404. Thank you so much.

4 (Whereupon, the above-entitled matter  
5 went off the record at 12:41 p.m. and resumed at  
6 1:32 p.m.)

7 CHAIR DRACKER: Okay. We will start  
8 the afternoon session. Marieann has an  
9 announcement first.

10 MS. BRILL: I am so sorry I have so  
11 many announcements today, but I was informed that  
12 the corrected slides for Lexapro are given to, I  
13 guess, our PAC members. Okay. And then David's  
14 slides will be posted on the website within 48  
15 hours, or let's just say next week. Thank you.

16 CHAIR DRACKER: Thank you, Marieann.  
17 We now have the FDA presentation on the summary  
18 of FDA completed review of pediatric safety  
19 issues and updated labeling for Exjade.

20 DR. WALDRON: Good afternoon. My name  
21 is Peter Waldron. I'm a pediatric hematologist  
22 in the Office of Surveillance and Epidemiology,

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1 and I'm the team leader for the Pediatric Safety  
2 Evaluation of deferasirox.

3 First, I will provide some background  
4 for the Committee, then I will present the  
5 Division of Pharmacovigilance's findings from the  
6 FDA Adverse Reporting System, or FAERS, and the  
7 literature. Then each of these groups will  
8 present their findings of this safety evaluation.

9 I will also provide a summary at the end.

10 deferasirox was approved for marketing  
11 in 2005 under the trade name Exjade for the  
12 indication of transfusional iron overload for  
13 ages two years and older. In 2009, the maximum  
14 dose was increased from 30 milligrams to 40  
15 milligrams for patients not adequately controlled  
16 with doses of 30 ml/kg per day.

17 In 2010, a box warning was added for  
18 renal failure, hepatic failure, and  
19 gastrointestinal hemorrhage. In 2013, Exjade  
20 received an additional indication for patients  
21 ages ten and older with non-transfusion-dependent  
22 thalassemia and chronic iron overload. For this

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1           indication, a maximum dose of 20 ml/kg per day  
2           was specified.

3                       In 2015, a new dose form of  
4           deferasirox, a filmcoated tablet, was approved  
5           under the trade name Jadenu. And in 2017, a  
6           granular form of Jadenu was approved. Due to  
7           increased bioavailability of the Jadenu form, a 7  
8           milligram dose of Jadenu is equivalent to 10  
9           milligrams of Exjade.

10                      In 2015, January, two years after the  
11           approval of the new indication for non-  
12           transfusion-dependent thalassemia for ages ten  
13           and older, a pediatric-focused safety review was  
14           performed. The findings of the review were  
15           presented to the PAC in September 2015.

16                      One of the cases presented was of a  
17           child from the U.S. with a fatal outcome. She  
18           was a 35-month-old girl with transfusion-  
19           dependent thalassemia who started transfusion at  
20           age seven months. She began chelation with  
21           Exjade at age 24 months. Her concomitant  
22           medications were multiple vitamins, vitamin D,

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1 and folic acid.

2 She was receiving a dose of Exjade  
3 greater than 30 ml/kg per day when her serum  
4 ferritin was less than 1,000 micrograms per  
5 liter. Her history indicated that she was at  
6 risk for acute hypovolemia due to diarrhea,  
7 vomiting, and possibly decreased oral intake, in  
8 addition to fever and association with a  
9 documented RSV infection.

10 She presented with acute kidney injury  
11 as indicated by serum creatinine value five times  
12 her baseline value and oliguria, as well as liver  
13 failure indicated by encephalopathy and  
14 coagulopathy. Later, she developed avert shock  
15 and respiratory failure. She died due to  
16 cerebral herniation.

17 During the public testimony at the  
18 September 2015 Pediatric Advisory Committee, the  
19 mother of the child who died gave testimony on  
20 her experience. Then a representative of the  
21 Cooley's Anemia Foundation testified about the  
22 membership's concern for use of Exjade during

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1 febrile illnesses and requested that a warning be  
2 added to the product information to stop the use  
3 of Exjade for children who develop a fever.

4 In November 2015, the Division of  
5 Pharmacovigilance was consulted based on the  
6 request from the PAC "to acquire any data  
7 regarding safety of continued medication to  
8 children who have fever and report back to the  
9 Committee." In April 2016, a tracked safety  
10 issued was open to facilitate participation of  
11 multiple disciplines within FDA to evaluate this  
12 safety concern.

13 In March 2017, I presented an interim  
14 report to the Committee. And in April 2018, the  
15 safety evaluation was complete. In May of this  
16 year, the deferasirox labels were updated.

17 The FDA staff who became involved in  
18 this safety issue were moved by the death of this  
19 child. At the same time, we were optimistic that  
20 we could improve the safe use of this drug among  
21 children, but, first, we needed to analyze the  
22 available data and perform additional analyses to

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1 develop the evidence necessary to support changes  
2 to the label.

3           These are the questions that we sought  
4 to answer in our effort to improve the safe use  
5 of deferasirox: Are there features of childhood  
6 illnesses, such as hypovolemia, that could  
7 interact with deferasirox use to produce severe  
8 toxicity? Could continued drug use during  
9 periods of decreased glomerular function result  
10 in increased drug exposure? And is there an  
11 interaction between drug dose and body iron  
12 burden such that, at a high body iron burden, a  
13 given dose may be associated with a lower rate of  
14 adverse actions, whereas that same dose at a  
15 lower body iron burden will be associated with an  
16 increased rate of adverse reactions?

17           Now I will present the Division of  
18 Pharmacovigilance's findings from FAERS and the  
19 medical literature for these safety concerns.  
20 You will note that the safety team expanded our  
21 evaluation beyond fever. Fever is a common event  
22 in the pediatric age group. As I presented in

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1 the interim report to the PAC in March 2017, we  
2 had evaluated clinical trial data and the  
3 literature and we found no support for an  
4 association between fever alone and any specific  
5 adverse event.

6 The safety team is very grateful to  
7 the family of the young girl who died for  
8 allowing us access to her medical records. That  
9 information, in combination with knowledge of  
10 pediatric illnesses and the known safety profile  
11 of deferasirox, guided our analyses to include  
12 dehydration or hypovolemia events in our  
13 evaluation.

14 This slide describes the well-known  
15 limitations of any database of spontaneous  
16 reports. Since you all have copies of the  
17 slides, I will spare you my reading of them.

18 This table is a summary of the  
19 findings of a FAERS search. All reports with an  
20 adverse event associated with deferasirox use  
21 were searched for reports with preferred terms  
22 associated with fever or dehydration. Then we

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1 reviewed the individual narratives to ensure that  
2 the case reported fever or hypovolemia. Those  
3 149 cases, confirmed cases, were then reviewed to  
4 determine which cases reported features  
5 indicating renal impairment. The most commonly  
6 reported indicators of renal impairment were  
7 serum creatinine elevation and proteinuria.

8 The median age of the 149 cases was  
9 eight years. Fifty-eight cases that reported  
10 fever only had the lowest rate of renal  
11 impairment, five percent. The 68 cases which  
12 reported only dehydration had a 25-percent rate  
13 of renal impairment, and the 23 cases which  
14 reported fever and dehydration had a 48-percent  
15 rate of indicators of renal impairment. These  
16 findings indicate a considerable rate of  
17 indicators of renal impairment with typical  
18 features of childhood illnesses.

19 In addition, the association between  
20 the severity of the risk factors for hypovolemia  
21 and the increased frequency of renal impairment  
22 suggest a dose effect of hypovolemia risk factors

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1 for indicators of renal impairment.

2 This table summarizes the findings of  
3 another FAERS search and literature reports of  
4 acute hepatic failure or hyperammonemia in  
5 children receive Exjade. Hepatic failure was  
6 defined as a case with a report of biochemical  
7 indicators of liver injury and mental status  
8 changes. Subsequently, cases were also  
9 characterized based on indicators of coagulation  
10 system function and on the presence of indicators  
11 of acute kidney injury, hypovolemia, and over-  
12 chelation.

13 The table includes thirteen FAERS  
14 reports and three literature cases which were not  
15 in the FAERS database at the time of the FAERS  
16 search. The median age of this group was five  
17 years, and the range was two years to fifteen  
18 years. One case did not report age. All FAERS  
19 reports describe findings of encephalopathy and  
20 four reported findings of coagulopathy. Two of  
21 the literature cases reported encephalopathy and  
22 all reported coagulopathy. Seven reports did not

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1 provide data that allow characterization of the  
2 coagulation system.

3 Cases that reported a prothrombin time  
4 greater than or equal to 30 seconds, an INR  
5 value greater than or equal to 2.0, or  
6 administration of plasma for coagulopathy were  
7 interpreted to demonstrate coagulopathy. Ten of  
8 the thirteen FAERS reports and two of the three  
9 literature reports described indicators of acute  
10 kidney injury. Cases that reported doubling of  
11 baseline serum creatinine, a statement of renal  
12 failure, or a report of renal replacement therapy  
13 were interpreted to demonstrate acute kidney  
14 injury.

15 All cases that reported criteria that  
16 allowed evaluation of risks for hypovolemia had  
17 that finding. Cases were interpreted to have  
18 risks for hypovolemia if they reported vomiting,  
19 diarrhea, or at least one day of anorexia.

20 Seven of the thirteen FAERS reports  
21 and all three of the literature reports described  
22 over-chelation. Six FAERS reports did not allow

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1 characterization of this criteria.

2 A report was interpreted to indicate  
3 over-chelation when the patient was receiving a  
4 dose of Exjade of greater than 25 ml/kg per day  
5 at a time when the serum ferritin was less than  
6 1,000 or a dose of Exjade greater than 20  
7 milligrams, sorry, greater than or equal to 20  
8 ml/kg per day at a time when the serum ferritin  
9 value was less than 500 micrograms per liter or a  
10 statement of discontinuation of all chelation  
11 following resolution of the acute event.

12 In summary, the DPV analysis found a  
13 high frequency of indicators of renal impairment  
14 among children with risk events for dehydration  
15 with or without fever and an association between  
16 risk factors for hypovolemia and the incidence of  
17 renal impairment indicators. Among the acute  
18 hepatic failure cases, most cases were  
19 characterized by severe acute kidney injury, risk  
20 factors for hypovolemia, and over-chelation.

21 The next speaker is Dr. Okusanya from  
22 the Office of Clinical Pharmacology who will

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1 discuss their findings of the interaction between  
2 renal function -- I don't know what happened.  
3 Okay. I didn't hit escape one time, but okay.  
4 He will be followed by Dr. Khurana, a pediatric  
5 nephrologist from the Division of Pediatric and  
6 Maternal Health, who will describe their  
7 evaluations of clinical methods for assessment of  
8 renal function and the application of those  
9 findings to d  
10 deferasirox dosing and monitoring during  
11 treatment. Last, Drs. Bird and Gelperin, who are  
12 members of the Division of Epidemiology, will  
13 report on their findings from clinical trial  
14 data. These reports include a nested case  
15 control study which evaluated the effects of  
16 Exjade dose and serum ferritin on the likelihood  
17 of acute kidney injury and findings from the  
18 sponsor's five-year registry which included  
19 children who were ages two to five at study  
20 initiation.

21 Dr. Okusanya.

22 DR. OKUSANYA: Thank you very much.

1 Good afternoon. My name is Lanre Okusanya, and  
2 I'm a clinical pharmacologist with the Division  
3 of Clinical Pharmacology V.

4 The Office of Clinical Pharmacology  
5 was consulted by the Division of  
6 Pharmacovigilance to help answer a few questions  
7 that arose during the deferasirox pediatric-focus  
8 safety evaluation. In this presentation, I will  
9 focus on two specific questions: one, what is the  
10 impact of deferasirox use on renal function; and,  
11 two, is there an exposure response relationship  
12 between deferasirox exposure and renal injury?

13 As mentioned by Dr. Waldron, several  
14 cases of renal dysfunction, including failure,  
15 has been observed in patients taking deferasirox.

16 As such, a box warning was placed on the label  
17 in January of 2010. As part of the box warning,  
18 a close patient monitoring is required,  
19 especially in patients with underlying renal  
20 disease.

21 Now, while we note that the elevation  
22 of serum creatinine patients on deferasirox is

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1 not uncommon, reversible decline in true renal  
2 function has been observed in children, as  
3 described by Dubourg, et al. And it showed that  
4 a decrease of approximately 20 percent, they  
5 showed it at approximately 20 percent in  
6 glomerular filtration rates, even in patients  
7 with normal renal function.

8 Now, despite the fact that deferasirox  
9 and its metabolites are primarily excreted by  
10 feces, renal impairment has an impact on  
11 deferasirox exposure. A comparison of the dose-  
12 normalized trough clearance in adult patients  
13 with varying degrees of renal impairment to those  
14 with normal renal function at week 13 and week 49  
15 of study US03, a single-arm trial in patients  
16 with myelodysplastic syndrome as shown in the  
17 figure above. We can see that there is a numeric  
18 increase in the dose-normalized trough  
19 concentrations with declining renal function,  
20 suggesting that patients with poor renal function  
21 may have higher deferasirox concentrations.

22 This impact of renal function of

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1        deferasirox concentration was also evaluated in  
2        pediatric patients using data provided by the  
3        sponsor from three different studies. This was  
4        evaluated using a linear mixed-effects model  
5        where eGFR, the estimated glomerular filtration  
6        rates as calculated using Schwartz equation was  
7        related to the log-transformed dose-normalized  
8        trough concentration. The impact of age, body  
9        surface area, underlying disease, gender, and  
10       race were also evaluated in the model.

11                The model showed a decline in eGFR was  
12        associated with increase in dose-normalized  
13        trough concentrations. For example, following a  
14        three-percent decrease in eGFR from 120 ml/min to  
15        80 ml/min, a 29-percent increase in trough  
16        concentration is predicted.

17                In addition to eGFR, body surface area  
18        was also a significant covariate, indicating that  
19        patients with small body surface areas had higher  
20        dose-normalized concentrations than patients with  
21        larger body surface areas. As such, a small  
22        change in eGFR in patients with small body

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1 surface areas is predicted to result in higher  
2 absolute trough concentrations in patients with  
3 higher body surface area.

4 Now, to further explore the clinical  
5 relevance of these increases in exposure, a  
6 relationship between deferasirox concentration  
7 and the probability of renal injury was explored.

8 The relationship between drug exposure and the  
9 probability of varying levels of renal injury  
10 were evaluated by the sponsor using the  
11 proportional odds model. The model modeled the  
12 odds of a patient worsening, that is the odds the  
13 patient worsening in their renal function or  
14 resulting in renal injury.

15 Now, the following renal injury  
16 categories were assessed: One, a greater than 25-  
17 percent increase in serum creatinine or urine  
18 protein-to-creatinine ratio grade on this line.  
19 Two, a greater or equal to 33-percent increase in  
20 serum creatinine or urine protein-to-creatinine  
21 ratio greater than 0.4. And, three, a serum  
22 creatinine greater than the upper limit of normal

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1 or urine protein-to-creatinine ratio greater than  
2 0.6.

3 Now, the analysis revealed a  
4 relationship between predicted trough  
5 concentrations and the risk for renal injury.  
6 Baseline elevation in serum creatinine, disease  
7 type, and time from the start of treatment were  
8 also found to be statistically-significant  
9 covariates. What was found was that a twofold  
10 increase in the trough concentrations, following  
11 a twofold increase in trough concentration, the  
12 estimated probability of patients' renal  
13 functions worsening was 1.52.

14 In summary, based on this analysis, we  
15 can conclude that deferasirox can cause renal  
16 injury. This is reflected in the black box  
17 warning that is currently on the label.  
18 Decreases in renal function can lead to increases  
19 in deferasirox concentrations, and higher  
20 deferasirox concentrations for an extended period  
21 of time can increase the probability of renal  
22 injury. This data is supportive of the findings

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1 to be presented by Dr. Bird and Dr. Gelperin.

2 DR. KHURANA: So one of our goals as  
3 part of the tracked safety issue was to identify  
4 areas where existing labeling language could be  
5 updated or strengthened to enhance the safety of  
6 deferasirox use in pediatric patients, especially  
7 those down to two years of age given the  
8 discussions at the 2015 PAC meeting about the  
9 index case. I'll be talking about the renal  
10 considerations we discussed when planning the  
11 safety analyses, which ultimately led to the  
12 deferasirox labeling changes which were  
13 implemented earlier this year.

14 This is the outline for my  
15 presentation. I'll briefly touch on the spectrum  
16 of renal toxicity reported with deferasirox use  
17 in both adults and pediatric patients. I'll then  
18 go into some of the challenges with monitoring of  
19 renal function that we considered when planning  
20 the analyses conducted by our safety evaluators,  
21 and I'll focus on the difficulties with relying  
22 on serum creatinine and creatinine clearance to

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1 guide drug dosing decisions and the utility and  
2 limitations of using prediction equations to  
3 estimate GFR. I'll end by highlighting the  
4 updated renal dosing and monitoring  
5 recommendations added to deferasirox labeling  
6 earlier this year as a result of our safety  
7 analyses.

8 So in pre-marketing clinical trials,  
9 transient elevations in serum creatinine and  
10 proteinuria were the most common renal adverse  
11 events reported. Post-marketing reports have  
12 subsequently described renal proximal tubular  
13 dysfunction and acute kidney injury of varying  
14 severity.

15 deferasirox is a known renal proximal  
16 tubular toxin, and the ensuing laboratory  
17 abnormalities really depend on the extent of  
18 tubular injury. Tubular injury can range from an  
19 isolated defect in one particular transporter to  
20 a global breakdown in solutransport known as the  
21 Fanconi syndrome.

22 And you can see from this slide that

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1 measurement of serum creatinine would not capture  
2 this type of tubular injury. So unless  
3 prescribers are actively monitoring their  
4 patients for these abnormalities, deferasirox-  
5 associated renal tubular toxicity could go  
6 undiagnosed.

7 So what are some of the challenges  
8 with monitoring renal function in the context of  
9 drug dosing? In current clinical practice,  
10 increases in serum creatinine and decreases in  
11 urine output over a short time frame are used to  
12 diagnose and stage acute kidney injury in both  
13 adults and pediatric patients. However, serum  
14 creatinine is known to be an insensitive marker  
15 of early renal injury, which makes reliance on  
16 acute changes in serum creatinine alone  
17 problematic from a dosing perspective, especially  
18 for drugs with a low therapeutic index.

19 You can see from this figure that a  
20 small increase in serum creatinine is initially  
21 associated with a large drop in GFR. And because  
22 of this relationship, waiting for the serum

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1 creatinine to increase by a certain percentage  
2 before reducing the dose or to greater than the  
3 upper limit of normal for age before interrupting  
4 the dose for a given drug may be too late if the  
5 goal is to prevent drug-related toxicity.

6 Another important limitation to the  
7 use of serum creatinine is the substantial intra-  
8 and interindividual variability typically seen  
9 with serum values.

10 Accurate interpretation of the serum  
11 creatinine is further complicated by the fact  
12 that normal values vary not only by sex and age  
13 but also by the type of serum creatinine assay  
14 used. Hopefully, you can see from this table  
15 that a value of 1 mg/dL derived by the enzymatic  
16 method would be considered the upper limit of  
17 normal for a 15 year-old boy but would exceed the  
18 upper limit of normal for a 15 year-old girl and  
19 would be two times the upper limit of normal for  
20 a five year-old boy.

21 Creatinine clearance has traditionally  
22 been used to estimate renal function, but it's

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1 important to note that creatinine clearance is  
2 not synonymous with GFR. Creatinine clearance is  
3 based on urinary creatinine which is not only  
4 filtered by the glomeruli but also secreted by  
5 the proximal renal tubule. And as a result,  
6 creatinine clearance values overestimate true GFR  
7 by that fraction of urinary creatinine that is  
8 derived from tubular secretion.

9 FDA has historically used the  
10 Cockcroft-Gault equation to estimate creatinine  
11 clearance for use in pharmacokinetic studies to  
12 determine drug dosing in adults with renal  
13 disease. The resulting values are expressed in  
14 ml/min and should be corrected for body surface  
15 area before being applied to pediatric patients.

16 Serum creatinine-based prediction  
17 equations are increasingly being used to overcome  
18 the interindividual variability associated with  
19 serum creatinine concentrations. These equations  
20 incorporate key demographic and clinical  
21 variables to account for variation in creatinine  
22 production among individuals. The MDRD and,

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1        increasingly, the CKD-EPI equations are used to  
2        estimate GFR in adults while the Schwartz  
3        equations are widely used to estimate GFR in  
4        children.

5                    The Schwartz equation was originally  
6        developed in 1976 to estimate GFR in children and  
7        relied on an older, less precise method for  
8        assaying serum creatinine. The equation was  
9        updated in 2009 to be used with standardized  
10       creatinine methods. Both equations rely on serum  
11       creatinine, height, and an empirical constant to  
12       estimate GFR corrected for body surface area in  
13       children.

14                   The utility of any prediction equation  
15       really depends on how well the estimated GFR  
16       value corresponds to true GFR in the population  
17       of interest. This figure shows mean measured GFR  
18       values corrected for body surface area in  
19       otherwise healthy children with mature renal  
20       function. And in general, measured values  
21       greater than 90 are considered to be normal.

22                   Although the Schwartz equations are

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1 commonly used to estimate GFR in children, these  
2 equations are not perfect and have limitations  
3 which must be considered when interpreting the  
4 eGFR values. Like other creatinine-based  
5 prediction equations, the Schwartz equations  
6 don't account for interindividual variability in  
7 creatinine production due to volume status,  
8 activity, and dietary protein consumption. They  
9 assume that serum creatinine is at steady state,  
10 which is not the case in the setting of acute  
11 kidney injury.

12 And, finally, it's also important to  
13 know that the updated Schwartz equation was  
14 developed in a pediatric chronic kidney disease  
15 population, so more data are still needed on how  
16 well this equation correlates with true GFR in  
17 children with more normal renal function.

18 The baseline serum creatinine  
19 concentration for any given individual represents  
20 a steady state when daily creatinine production  
21 equals daily urinary creatinine excretion. eGFR  
22 values derived from the Schwartz equations can

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1 over or underestimate true GFR if the baseline  
2 serum creatinine is impacted by factors which can  
3 tip this balance in any one direction.  
4 Overestimation of true GFR is a possibility for  
5 patients with low baseline serum creatinine  
6 values. These patients have lower than normal  
7 daily creatinine production due to reduced muscle  
8 mass or malnutrition from their underlying  
9 disease.

10 Underestimation of true GFR is  
11 possible when there's some other reason for the  
12 baseline serum creatinine to be elevated. And,  
13 finally, chronic anemia can induce changes in  
14 renal blood flow that can actually increase GFR,  
15 so it's unclear how well eGFR corresponds with  
16 true GFR in the thalassemia population in whom  
17 chronic anemia is likely to be highly prevalent.

18 We applied many of the concepts I've  
19 just shared with you in planning and conducting  
20 the analyses you've heard and will hear from our  
21 safety evaluators. Because the goal of our  
22 safety analyses was to inform drug dosing in

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1 product labeling, we've relied on eGFR values  
2 derived from the Schwartz equations as the basis  
3 for the exposure response analyses and the  
4 analysis of the Five-Year Pediatric Registry, as  
5 well as to define cases and controls in the  
6 nested case control study.

7 Based on our safety analyses, we  
8 identified several areas where labeling could be  
9 updated to mitigate the risk of renal toxicity in  
10 pediatric patients, and I'll briefly highlight  
11 some of these areas in my remaining slides.

12 As Dr. Waldron mentioned, post-  
13 marketing reports prompted FDA to add a box  
14 warning to deferasirox labeling in 2010. The box  
15 warning cautioned prescribers about the  
16 possibility of acute renal failure and death with  
17 product use, particularly in patients with co-  
18 morbidities, and recommended dosage adjustments  
19 based on changes in serum creatinine.

20 The box warning was updated earlier  
21 this year to emphasize reliance on changes in  
22 eGFR to guide drug-dosing decisions and more

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1 frequent monitoring and increased vigilance of  
2 patients with baseline renal impairment or with  
3 one or more risk factors for acute kidney injury,  
4 including pediatric patients with volume  
5 depletion or over-chelation.

6 Prior labeling language  
7 contraindicated product use in patients whose  
8 serum creatinine was more than two times the  
9 upper limit of normal or who had a creatinine  
10 clearance less than 40. Updated labeling now  
11 contraindicates use in all patients two years of  
12 age and older with an eGFR less than 40. Prior  
13 labeling informed prescribers to initiate therapy  
14 based on serum creatinine and creatinine  
15 clearance and to reduce the starting dose by 50  
16 percent in patients with baseline renal  
17 impairment as defined by creatinine clearance.

18 Updated labeling provides initial  
19 dosing recommendations based on eGFR derived from  
20 age-appropriate prediction equations and includes  
21 language informing prescribers to look for both  
22 tubular and glomerular dysfunction prior to

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1 initiating therapy. Current labeling also  
2 includes more detailed language about dose  
3 interruption in pediatric patients with volume  
4 depletion due to an acute intercurrent illness,  
5 as well as the importance of continued monitoring  
6 of tubular and glomerular function during  
7 therapy, and to reevaluate the risk-benefit  
8 profile of continued deferasirox use in the  
9 presence of either type of renal injury.

10 I'd like to acknowledge these members  
11 of the Division of Pediatric and Maternal Health  
12 who helped me with this presentation. Thank you.

13 DR. BIRD: I'm going to be giving a  
14 presentation on analysis of pediatric clinical  
15 trial data.

16 So through an information request to  
17 Novartis, clinical study data sets were obtained  
18 for deferasirox-treated pediatric patients. The  
19 pooled clinical data sets included company-  
20 sponsored interventional and perspective  
21 observational clinical studies. Ten studies were  
22 identified that included pediatric patients with

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1 perspective collection of clinical laboratory  
2 data and all data presented here for Exjade  
3 because the pooled clinical trial data sets  
4 contained very few patients receiving Jadenu for  
5 transfusion-dependent thalassemia.

6 So there's two objectives we'll be  
7 presenting today. The first is to investigate  
8 whether relatively high deferasirox dose and  
9 relatively lower body iron burden as measured by  
10 serum ferritin, either together or independently,  
11 increased the risk for acute kidney injury. The  
12 second is to determine whether the exposure-  
13 adjusted incidence rates of clinical adverse  
14 events are increased when Exjade dose is greater  
15 than 25 mg/kg per day, while serum ferritin is  
16 concurrently less than 1,000 micrograms per  
17 liter.

18 So first I'll be presenting the pooled  
19 analysis of clinical laboratory data. So,  
20 overall, we identified 1367 pediatric patients in  
21 the pooled clinical studies. We excluded 117  
22 that were either less than two years of age or

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1 didn't have a diagnosis of transfusion-dependent  
2 thalassemia, and we excluded an additional 37  
3 patients that didn't have sufficient laboratory  
4 data for analysis. This left the 1213 patients  
5 that contributed 162 cases of acute kidney injury  
6 and 621 matched controls that had normal renal  
7 function. So it was a very high-level summary of  
8 the study design.

9 Renal function was assessed monthly in  
10 most patients using the estimated glomerular  
11 filtration rate, or eGFR. Acute kidney injury  
12 cases were defined as an eGFR less than or equal  
13 to 90 among patients with normal baseline renal  
14 function. Controls were defined as an eGFR  
15 greater than or equal to 120, dosage in mg/kg per  
16 day, and serum ferritin in micrograms per liter  
17 were available throughout follow-up, and the  
18 analysis was conducted using conditional logistic  
19 regression.

20 So this slide summarizes the findings  
21 for the effect of Exjade dose on a risk for acute  
22 kidney injury. First, we found that a 26-percent

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1 increased kidney injury risk was observed per  
2 five mg/kg per day increase in Exjade dosage  
3 above the typical starting dosage of 20 mg/kg per  
4 day. Larger acute kidney injury risk was  
5 observed above larger dose thresholds with a 73-  
6 percent increased risk above the threshold of an  
7 Exjade dose greater than 30.

8 This slide summarizes the effect of  
9 serum ferritin on risk for kidney injury. First,  
10 we found that a 25-percent increased acute kidney  
11 injury risk was observed per 250 microgram per  
12 liter decrease in serum ferritin starting at 1250  
13 microgram per liter. Larger risk was observed  
14 below decreasing serum ferritin thresholds with  
15 an 85-percent increased risk below the threshold  
16 of less than 1,000 microgram per liter.

17 This slide depicts the combined  
18 effects of having both a serum ferritin less than  
19 a thousand while Exjade dose is greater than 30.

20 High-dose deferasirox resulted in a 4.47-fold  
21 increased risk for a kidney injury in pediatric  
22 patients when serum ferritin was less than a

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1 thousand. Even when serum ferritin was greater  
2 than a thousand, a 1.67-fold increased risk for  
3 kidney injury was observed at high-dose  
4 deferasirox, consistent with dose-related  
5 nephrotoxicity. Low serum ferritin values less  
6 than a thousand observed a 4.08-fold increased  
7 risk for kidney injury among patients taking  
8 high-dose deferasirox, and the effect of low  
9 serum ferritin was also non-significantly  
10 elevated among patients not receiving high-dose  
11 deferasirox.

12 This slide shows the effect of age on  
13 risk for kidney injury. Overall, you can see  
14 that there was a numerically-larger risk observed  
15 in younger pediatric patients two to six years  
16 versus seven to fifteen years. However, the  
17 differential risk by age did not achieve  
18 statistical significance.

19 Finally, here's a summary of cases of  
20 acute kidney injury and there disposition. So  
21 acute kidney injury cases had a mean 50.2 percent  
22 eGFR decrease from baseline compared with a 6.9

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1 percent eGFR decrease in controls. Most kidney  
2 injury cases, 95.7 percent, had a documented  
3 recovery to an eGFR greater than 100. After the  
4 initial episode, deferasirox treatment was  
5 discontinued in 11 patients and the dose was  
6 decreased in 12 patients. And the among patients  
7 who recovered from kidney injury, 62 had a  
8 subsequent episode of kidney injury of whom 30  
9 patients had a third episode and 16 patients had  
10 four or more episodes of kidney injury during  
11 follow-up.

12 So next Dr. Kate Gelperin is going to  
13 present the results of our second objective, too.

14 DR. GELPERIN: In addition to the  
15 analysis of clinical laboratory data just  
16 described by Dr. Bird, the study team conducted  
17 an analysis of clinical adverse events in  
18 pediatric thalassemia patients from the pooled  
19 data set who received an Exjade dose greater than  
20 25 ml/kg per day when their serum ferritin was  
21 less than a thousand micrograms per liter.

22 We calculated incident rate ratios

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1 comparing the incidence of adverse events during  
2 the first period when simultaneous criteria for  
3 high-dose and low serum ferritin were met with  
4 the preceding study period for each of the 157  
5 patients who met the simultaneous criteria for  
6 dose and serum ferritin at least once.

7 Clinical adverse events were reported  
8 by study site investigators and tabulated using  
9 MedDRA codes. Overall, the incidence of adverse  
10 events and serious adverse events was generally  
11 higher during periods when patients with low  
12 serum ferritin received Exjade dose greater than  
13 25 ml/kg per day. The effect was most striking  
14 for adverse events coded within the renal and  
15 urinary disorder system organ class with a  
16 significant six-fold increased risk.

17 Adverse events of special interests as  
18 defined by the sponsor, as well as adverse events  
19 necessitating dose interruption, occurred about  
20 twice as often during periods when the  
21 simultaneous criteria for dose and ferritin were  
22 met compared to the previous study periods.

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1           A five-year pediatric registry was  
2 conducted by Novartis in fulfillment of the  
3 Subpart H post-marketing study commitment issued  
4 at the time of approval to obtain additional  
5 safety information on deferasirox in young  
6 pediatric patients. The final study report was  
7 submitted to FDA in 2016, and those data were  
8 included in this pooled analysis of clinical  
9 studies.

10           In addition, clinical laboratory data  
11 from the five-year registry were analyzed to  
12 evaluate changes in kidney function over time in  
13 children who were two to less than six years old  
14 at the time of study entry. Serum creatinine was  
15 measured monthly in most patients. However,  
16 comparison of serum creatinine values with local  
17 reference ranges was found not to be a sensitive  
18 indicator of kidney injury and many study sites  
19 reported reference ranges that may not have been  
20 age appropriate.

21           As you heard from Dr. Khurana today,  
22 there are some issues with relying on unadjusted

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1 serum creatinine values to detect kidney injury,  
2 especially in pediatric thalassemia patients who  
3 may have low muscle mass and chronic glomerular  
4 hyperfiltration. For these reasons, serum  
5 creatinine values in pediatric thalassemia  
6 patients are often abnormally low, even in the  
7 presence of kidney injury. To address this  
8 issue, we evaluated eGFR values over time in  
9 registry patients as calculated with the  
10 appropriate Schwartz equations to take body size  
11 into account.

12 Of the 267 pediatric patients enrolled  
13 in the five-year registry, 242 patients had pre-  
14 and post-baseline eGFR measurements. Of these,  
15 116 patients had a decrease in eGFR of at least  
16 33 percent observed at least once. Twenty-one of  
17 these 116 patients, that's 18 percent, had a dose  
18 interruption and an additional 15 patients had a  
19 dose decrease within 30 days. This analysis  
20 showed that acute kidney injury could cause  
21 increased deferasirox levels and potential  
22 exposure related toxicity commonly in young

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1 children participating in the five-year registry  
2 and often was followed by a dose decrease or  
3 interruption of therapy.

4 Acute kidney injury risk was markedly  
5 elevated when relatively high deferasirox dose  
6 was administered to pediatric patients with  
7 relatively low body iron burden measured to serum  
8 ferritin. The findings of our analyses support  
9 the role of over chelation as a causative factor  
10 for acute kidney injury among pediatric patients  
11 receiving deferasirox.

12 The pharmacokinetic data presented  
13 today by Dr. Okusanya showed that even relatively  
14 small decreases in eGFR are associated with  
15 significantly increased deferasirox plasma  
16 concentrations. Because deferasirox-induced  
17 nephrotoxicity is dose related, increased drug  
18 plasma concentrations can exacerbate kidney  
19 injury and lead to escalating toxicity.

20 I would like to acknowledge the study  
21 team who worked on the pooled analyses and  
22 especially Fang Tian and Scott Swain who were our

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1 data analysts.

2 DR. WALDRON: In summary, this was a  
3 safety review in response to requests from the  
4 Committee following the report of the death of an  
5 almost three-year-old child who was receiving a  
6 dose of Exjade greater than 30 ml/kg per day when  
7 her serum ferritin was less than 1,000. We had  
8 an antecedent illness with risks for hypovolemia  
9 and who subsequently developed acute kidney  
10 injury and failure and hepatic failure.

11 The findings of the safety review team  
12 with direct relevance to this case are: There's a  
13 risk of renal impairment associated with acute  
14 illnesses that have risks for volume depletion,  
15 decreased renal function results in increased  
16 deferasirox exposure and increased exposure  
17 results in decreased renal function with a  
18 potential for an exacerbating cycle and possibly  
19 hepatic toxicity, and there is a risk of acute  
20 liver failure in children receiving deferasirox.  
21 The risks of high-deferasirox dose and low serum  
22 ferritin as a measure of body iron are additive

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1 for the development of diminished renal function.

2 There is also a risk of life-threatening adverse  
3 events when full-dose Exjade is continued at a  
4 time when the body iron burden is approaching or  
5 within the normal range.

6 Based on the findings, the agency  
7 entered discussions with the sponsor to modify  
8 the deferasirox labels with the intention to  
9 improve safe use. The label changes are  
10 summarized here, followed by the sections of the  
11 label where these changes were applied. These  
12 label updates include the modifications related  
13 to hypovolemia events; the relationship between  
14 plasma drug levels and eGFR; the recommendation  
15 to use eGFR rather than serum creatinine during  
16 drug initiation and monitoring; the risk of life-  
17 threatening organ injury when the full  
18 deferasirox doses, when full-dose deferasirox for  
19 transfusional iron overload are used while the  
20 serum ferritin values are approaching the normal  
21 range; the use of serum ferritin value of less  
22 than 1,000 as a measure of body iron to indicate

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1 a need for reevaluation of dose and/or monitoring  
2 regimen and the related added statement to use  
3 the minimum effective dose to maintain iron  
4 burden in the target range; the interaction  
5 between dose, serum ferritin, and the risk of  
6 renal impairment; and, finally, the increased  
7 risk of auditory impairment when the over-  
8 chelation criteria are met.

9 These are the members of the safety  
10 issue team, and that is the end of our  
11 presentation.

12 CHAIR DRACKER: Thank you to all of  
13 you for that presentation. We will now proceed  
14 with panel discussions. There will not be a vote  
15 at the end of these discussions. I would like to  
16 remind the public observers that while this  
17 meeting is open for public observation, public  
18 attendees may not participate except at the  
19 specific requests of the panel.

20 Please, again, mention your name and  
21 affiliation, please. Thank you.

22 MEMBER HOEHN: Sarah Hoehn, Advisory

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1 Committee. I had a question for Dr. Bird. When  
2 you were talking about the stage 4 kidney injury,  
3 I wondered if there was any data on anyone who  
4 progressed to needing dialysis or a renal  
5 transplant or any evidence about anyone who had  
6 permanent kidney injury.

7 DR. BIRD: We didn't have any of that  
8 data in the full data set. We did lose some  
9 patients to follow up, but we can't comment on  
10 that any further.

11 MEMBER HAVENS: Is there information  
12 on proteinuria? It seems like there's a lot of  
13 confusion about how to interpret pediatric  
14 creatinine measurements and perhaps a dipstick  
15 protein would be easier for people to interpret  
16 if proteinuria occurs as a part of this renal  
17 injury since it seems to be tubular.

18 DR. KHURANA: Proteinuria was included  
19 as part of the assessment in the NDA. I can't, I  
20 would have to defer to Dr. Gelperin if it was  
21 included in the data. I would defer to our  
22 safety evaluators for their respective analyses

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1 about whether that was a component, proteinuria,  
2 urine protein and creatinine.

3 DR. OKUSANYA: So in the exposure  
4 response evaluation for renal injury, proteinuria  
5 and/or increase in serum creatinine was also  
6 evaluated. It was an and/or evaluation, so I  
7 don't think there were a lot of patients that had  
8 elevated proteinuria.

9 DR. KHURANA: I just wanted to make  
10 the additional comment that the assessment of  
11 proteinuria is also challenging, particularly  
12 with this drug, because it's a known tubular  
13 toxin. And so distinguishing whether it's  
14 tubular in origin versus glomerular would also be  
15 a challenge with the information we have  
16 available.

17 MEMBER OSTER: So just two comments.  
18 The first one is the death of the three-year-old,  
19 there was a mention of her taking multivitamins.  
20 And when I look at the labeling and the  
21 recommendations, I think there's been tremendous  
22 work here and thank you for that, but I didn't

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1 see anything talking about maybe warning people  
2 not to give the children multivitamins or to  
3 think about the food intake and iron, not that  
4 kids love spinach but you never know. And so  
5 that's just one comment about the multivitamins  
6 that I didn't see.

7 And the second one is on dehydration.

8 I don't know how mobile these children are, but,  
9 if they are running around on a hot sunny day I  
10 didn't see anything in the write-up to say that,  
11 again, sports and dehydration should be  
12 monitored, as well.

13 DR. WALDRON: You're correct that we  
14 did not evaluate multiple vitamins, and we felt  
15 that that was outside of the scope of our review.

16 And often those are not considered to be drugs,  
17 and so, frequently, they're not even reported as  
18 part of a concomitant medication. There are  
19 studies in adults that question the value of  
20 multiple vitamins, but I'll just leave that  
21 alone. Go ahead.

22 MEMBER OSTER: I just wanted to -- and

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1 that's fine, but, because the reading, it said  
2 that just when we get to that normal, you know,  
3 normal state that the iron level is so critical,  
4 I just, you know, you never know, is the kid  
5 taking a Flintstone with iron? And so I just  
6 bring it up, even though it hasn't been studied,  
7 that might be something worth mentioning.

8 DR. WALDRON: It might be helpful to  
9 keep in mind that these are children who are  
10 getting transfused, which represents a very large  
11 amount of iron coming into the body every three  
12 to, roughly, five week --

13 MEMBER OSTER: I was thinking about  
14 that when I was making the comment, but I just  
15 felt, because it looked to me, granted coming  
16 from a non-medical background, that little  
17 changes can make a big difference. I just felt I  
18 wanted to bring it up.

19 DR. WALDRON: And there are, for the  
20 non-transfusiondependent thalassemia children,  
21 there are recommendations that there are multiple  
22 vitamins, if you choose to use multiple vitamins,

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1 that don't have extra iron, and so that is  
2 something that practicing hematologists often  
3 recommend to their patients.

4 And regarding dehydration, you know,  
5 we cited the things that are maybe the most  
6 obvious and the most easy to ascertain from the  
7 adverse event reports, those events of vomiting,  
8 diarrhea, and anorexia, but we could not control  
9 whether you're in Minnesota or Alabama in June,  
10 you know, so we couldn't do that level of  
11 analysis.

12 MEMBER WADE: Kelly Wade. This was  
13 really excellent and really wonderful to have  
14 this much data. I'm wondering if, over the past  
15 maybe two years, if there have been any reports  
16 in the FAERS about liver failure or renal  
17 failure. Have these cases stopped coming into  
18 the FAERS? And then I also wonder in just kind  
19 of an aggregate of looking at maybe pharmacy data  
20 or any of your data sets do we know if  
21 prescribers are limiting the dose that's being  
22 prescribed? Like as we associate with these

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1 higher doses, do you have any pharmacy data or  
2 anything that says perhaps hematologists are  
3 aware of these warnings?

4 DR. WALDRON: I'll answer the first or  
5 the second question first. The label change just  
6 occurred in May of this year and so four months  
7 ago, and in the end of August Novartis, the  
8 sponsor, sent "Dear Healthcare Provider" letters  
9 to a large number, I think it was in the  
10 neighborhood of 10,000 providers. So they've  
11 certainly made a good faith effort to raise the  
12 awareness of all of these relevant label changes.

13 Typically, we would not get that level  
14 of data to say that we know the dose in terms of  
15 milligrams per kilogram per day that a prescriber  
16 would get, so I don't think that we would be able  
17 to answer that or whether anyone else wants to  
18 make a comment on that.

19 But your first question of has this  
20 stopped, Dr. Crew who is sitting at the table  
21 over there was involved in the original FAERS  
22 search and then did an update because it had been

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1 two years from the original search. And at that  
2 time, there was one additional patient who was an  
3 adolescent and had this exact picture of high-  
4 dose low-body iron renal failure and hepatic  
5 failure. And so, you know, that was prior to the  
6 labeling update, of course. We're optimistic,  
7 but, you know, sometimes the word gets out and  
8 it's practice, sometimes it isn't. So we'll have  
9 to wait and see at this point.

10 MEMBER HOEHN: This is a follow-up to  
11 the two other questions. I think it's awesome  
12 all the work that's been done in terms of raising  
13 awareness and education, but I wondered if there  
14 were any specific documents targeted towards the  
15 family, like an informed consent or anything they  
16 had to sign, because I'm sure a lot of children  
17 get viral illnesses and get mild dehydration and  
18 they don't necessarily call their pediatrician  
19 every single time. So I didn't know if there  
20 were any specific family documents that were  
21 created to go to the families or any specific  
22 consent for families so they acknowledge that

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1 they're aware of the risks of dehydration.

2 DR. WALDRON: Of course, consent is at  
3 a practitioner level and it's not something that  
4 the agency has any influence over. And I will  
5 ask the Deputy Director for Safety, Barry Miller,  
6 as far as I recall, there was no modification of  
7 the med guide. That was my recollection. Could  
8 you confirm? And I think that's responsive to  
9 your question.

10 CHAIR DRACKER: Use the microphone,  
11 please. Just identify yourself, please.

12 MR. MILLER: Barry Miller from the  
13 Division of Hematology Products. Exjade, you're  
14 right, does not have a medication guide. That  
15 would be the sort of setting, that would be the  
16 sort of information for a patient's family  
17 members. There is, in Section 17 of the label  
18 there is a guidance for the prescriber to educate  
19 the parents, and that's where the information  
20 would be in there. I mean, that is something we  
21 considered discussing with the sponsor.

22 CHAIR DRACKER: Thank you. Do you

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1 have another question? No? Okay. Anyone else?

2 Okay. We will take a 15-minute break, and then  
3 we'll resume and have two informational sessions.

4 Thank you.

5 (Whereupon, the above-entitled matter  
6 went off the record at 2:32 p.m. and resumed at  
7 2:57 p.m.)

8 DR. DRACKER: And we have two FDA  
9 presentations, which are informational only.  
10 There will be no discussions. The first is an  
11 update on the safety of long-acting beta agonist  
12 or LABAs, which I love that acronym.

13 Thank you. All right.

14 DR. LIM: So, good afternoon. My name  
15 is Robert Lim. I am a pediatric pulmonologist  
16 and a clinical team leader in the Division of  
17 Pulmonary, Allergy, Rheumatology Products. And  
18 in my presentation today I'll just be giving an  
19 update on the safety of long--acting beta  
20 agonists and asthma.

21 Here is an outline of my presentation.

22 I'll first begin with some background on the

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1 LABA safety issue, followed by a discussion on  
2 the LABA safety trials, as well as well as their  
3 individual results, as well the results of the  
4 FDA meta-analysis of those LABA safety trials.  
5 And, this will be followed by the effect that  
6 these have had on the labeling. And then, a  
7 summary of my presentation.

8 So, as of most of you know, there's  
9 been a longstanding ---- there have been  
10 longstanding LABA safety concerns regarding  
11 increased risk of serious asthma outcomes, such  
12 as asthma related hospitalizations, intubations,  
13 and deaths. And these concerns initially stemmed  
14 from the results of the Serevent Nationwide  
15 Surveillance study or SNS.

16 And we're again raising the Salmeterol  
17 Multicenter Asthma Research Trial or SMART. Due  
18 to these safety concerns, the FDA also performed  
19 a meta-analysis back then, which raised similar  
20 concerns and also showed a potential increase  
21 risk of hospitalization in pediatric patients.

22 Due to these concerns there is an

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1 extensive regulatory history, with multiple  
2 advisory committee meetings, labeling change ----  
3 and the labeling changes, which ultimately  
4 resulted in a box warning for all LABA containing  
5 products.

6 The FDA also required large post-  
7 marketing in safety trials to evaluate the risk  
8 of LABA when added to ICS. And these trials are  
9 complete.

10 This slide summarizes the results of  
11 via FDA's previous meta-analysis, which led to  
12 the pediatrics safety concern regarding asthma  
13 related risks in that population. And, based on  
14 that meta-analysis that was previously done,  
15 there appeared to be a trend for increased risk  
16 for serious asthma outcomes with the decreasing  
17 age.

18 The next couple of slides will  
19 summarize a relevant regulatory history. I'll  
20 start with some important milestones, starting  
21 back in the 90's and then spanning through early  
22 2005.

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1           The green boxes show the LABA products  
2 approved for asthma around this time. The first  
3 LABA approved for -- was salmeterol inhalation  
4 aerosol in 1994. Then, around 2001 -- 2000,  
5 2001, the first ICS/LABA combination product was  
6 approved, as well as the first formoterol  
7 product.

8           The blue arrows represent the large  
9 safety studies with salmeterol as stated in the  
10 previous slide. Data from these studies showed  
11 an increased risk in serious asthma outcomes with  
12 the use of LABA.

13           SMART also showed potential that  
14 African Americans may be at increased risk. The  
15 result of these trials led to a box warning on  
16 salmeterol and an advisory committee meeting in  
17 2005 to discuss those results.

18           This brings us from 2005 to the  
19 present. During this period of time, there were  
20 multiple new ICS/LABA combinations approved shown  
21 here in these green boxes. There are also  
22 multiple advisory committee meetings and

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1 regulatory activities stemming from the LABA  
2 safety concerns.

3           Following the 2005 Pulmonary Allergy  
4 Drug Advisory Committee, box warnings and  
5 medguides were required on all LABA containing  
6 products, the results of SMART were also included  
7 in product labeling.

8           Following the 2008 advisory committee  
9 meeting, FDA required further safety labeling  
10 changes in -- as well as a risk evaluation  
11 mitigation strategy and required post-marketing  
12 clinical trials, which I'll be -- we've all just  
13 referred to as the LABA safety trials.

14           The design of these trials was  
15 discussed at the 2010 PADAC meeting. And the  
16 blue arrow represents the LABA safety trials with  
17 the final reports submissions staggered between  
18 2016 and 2017.

19           The review of which ultimately led to  
20 further product labeling changes, including the  
21 removal of the box warnings for the ICS/LABA  
22 products indicated to treat asthma. In the next

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1 slides, I'll discuss the required LABA safety  
2 trials.

3 So, as you're aware, FDA required each  
4 sponsor of a LABA containing product approved for  
5 asthma to conduct a large safety trial. These  
6 trials were ---- these large trials were  
7 important to the FDA, as well as the community.  
8 And the design of these trials were discussed in  
9 an AC meeting in 2010. And the protocols were  
10 finalized in 2011.

11 The objective was to evaluate the  
12 safety of LABA when added to ICS. And the  
13 outcome of interest was serious asthma outcomes  
14 defined as asthma related hospitalizations,  
15 intubations, and deaths. Given the rarity of  
16 asthma death, at the time of the design, we  
17 anticipated that the results would be driven by  
18 hospitalizations.

19 These trials are ---- also included  
20 efficacy set ---- efficacy assessments, which  
21 were primarily exacerbation. We had particular  
22 interest in including patients less than 18 years

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1 of age in these trials given the previously  
2 alluded to pediatrics safety concerns.

3 These required studies were all  
4 similar in design to allow for pooled safety  
5 analyses for rare events such as asthma related  
6 deaths and intubation. And, to that end, the  
7 sponsors worked together on study conduct and  
8 shared a joint oversight steering committee and a  
9 joint data monitoring committee. Asthma  
10 relatedness was also adjudicated by a shared  
11 committee.

12 This slide summarized the required  
13 studies in adolescents and adults. There were  
14 four concurrent studies, 26 weeks in length, with  
15 each of those products listed here.

16 Each trial enrolled around 11,700  
17 patients aged 12 years and older with asthma. At  
18 least ten percent of patients were required to be  
19 12 to 17 years of age so that we would get data  
20 on that population.

21 And the treatment groups were ICS/LABA  
22 versus ICS. The primary in point was serious

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1 asthma outcomes defined as asthma related  
2 hospitalizations, intubations, and deaths.

3 These trials were all non-inferiority  
4 in design. And, each trial was individually  
5 powered to have 90 percent power to rule out a  
6 two fold increase in event rate.

7 Given the specific concerns regarding  
8 pediatrics safety, a separate LABA safety study  
9 in patients 4 to 11 years of age was required.  
10 This study was for Advair as this was the only  
11 ICS/LABA product approved for this age group.

12 The design was overall similar to  
13 adults with the following notable differences.  
14 First, the trial was smaller. It only included  
15 6,200 patients and obviously the patient  
16 population was different with the patients being  
17 4 to 11 years of age. Additionally, this ----  
18 because of the smaller size, this provided power  
19 ---- this provided 90 percent power to rule out a  
20 2.7 fold increase in event rate.

21 In all LABA safety trials, efficacy  
22 was also evaluated in terms of exacerbations,

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1 where each exacerbation was defined as  
2 deterioration asthma requiring the use of  
3 systemic corticosteroids, in-patient  
4 hospitalizations, or an emergency department  
5 visit requiring systemic steroids.

6 The trials were completed in a  
7 staggered manner and submitted to the FDA. The  
8 approximate dates for their completion are shown  
9 here in this slide. It's worth noting that  
10 Novartis withdrew from formoterol fumarate from  
11 the U.S. market and so terminated their LABA  
12 safety study.

13 Overall, each completed trial excluded  
14 the prespecified noninferiority margin and there  
15 were very few events of intubations and deaths  
16 across all trials. There were also significant  
17 decreases in protocol defined as asthma  
18 exacerbations, which were primarily driven by  
19 events requiring systemic steroids.

20 The numerical results for the safety  
21 analysis are summarized in this slide. Across  
22 the top are the individual trials and the columns

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1 are the results for serious asthma outcomes  
2 overall, and then broken down by their individual  
3 components.

4 First, I'd like to draw your attention  
5 to the results from the adolescent and adult  
6 trials, boxed in red. As you can see, the hazard  
7 ratios were around 1 with 95 percent confidence  
8 intervals excluding the prespecified  
9 noninferiority margin of 2.

10 Results for the pediatrics Advair  
11 study also demonstrated a hazard ratio of around  
12 1 with 95 percent confidence intervals, excluding  
13 the prespecified margin of 2.7. As previously  
14 noted however, there were very few deaths or  
15 intubations and the outcome was driven primarily  
16 by asthma related hospitalizations.

17 A meta-analysis was also performed  
18 using the adult adolescent data. The results of  
19 the meta-analysis are summarized in this table.  
20 And, consistent with the individual studies, the  
21 hazard ratio for the meta-analysis is right  
22 around 1 with an upper limit of the 95 percent

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1 confidence intervals of 1.44.

2 Overall, the data from the individual  
3 studies and meta-analysis did not show  
4 significant increase in risk of serious asthma  
5 related events with ICS/LABA fixed dosage  
6 combination compared to ICS alone. Though these  
7 trials were not designed to rule out all risk for  
8 serious asthma related events.

9 As we had the pediatric safety  
10 concern, this slide summarizes these subgroups --  
11 -- summarizes subgroup analysis by age, broken  
12 down by 12 to 17, 18 to 64, and greater than 64.

13 And these results are consistent for each age  
14 group with the primary analysis and do not  
15 suggest an increased risk with decreasing age.

16 In this slide, I've just shown the  
17 basically the same graphically. For each of the  
18 adolescent adult trials and then the  
19 meta-analysis of the adolescent adult trials and  
20 then the lowest row is the Advair pediatric  
21 trial.

22 With regard to efficacy, in the

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1 adolescent adult studies, a statistically  
2 significant reduction in asthma exacerbations  
3 were observed for ICS/LABA versus ICS alone.  
4 And, in the pediatrics study, a similar trend was  
5 observed, just missed things, statistical  
6 significance.

7 So, as a result of these data  
8 analyses, the FDA openly removed the box warning  
9 from the ICS/LABA products. The warnings were  
10 also revised to emphasize the risk of LABA  
11 monotherapy and to describe the results from  
12 these trials and the meta-analyses.

13 As the box warning was removed, the  
14 medguide was also changed to a patient  
15 information leaflet and although these trials  
16 were ---. And although when these trials were  
17 initially required, as like excuse me---

18 Although we had initially planned to  
19 take this to AC when these trials required, the  
20 FDA, given the nature of the results, how they  
21 were relatively clean across all studies, and in  
22 the interest of expediency, this action was taken

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1 without an advisory committee meeting.

2 So, this action effected the labeling  
3 of six products including those products, which  
4 were not included in the LABA safety trials.  
5 These products are listed in this table.

6 The grayed out rows are for those  
7 products which did not conduct their own LABA  
8 safety study. For the single ingredient LABA  
9 products listed here, the labeling on the box  
10 warning are entirely unaffected.

11 And so, in summary the required LABA  
12 safety studies all met the prespecified  
13 non-inferiority margins in the FDA combined  
14 analysis. Not surprisingly, the findings were  
15 similar. And additionally, sub-group analyses  
16 across multiple sub-groups were consistent with  
17 the overall analyses.

18 ICS/LABA treatment also resulted in  
19 decreased exacerbations compared to ICS alone for  
20 the studied products. And given these data, the  
21 box warning was removed from the ICS/LABA  
22 contained products, which were indicated to treat

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1 asthma. Thank you.

2 DR. DRACKER: Okay, thank you very  
3 much for the presentation. Next we have a  
4 discussion on gadolinium.

5 DR. FOTENOS: Good afternoon and  
6 welcome to the end of your long meeting day. My  
7 name is Anthony Fotenos and I'm a Medical Officer  
8 in the Division of Medical Imaging Products.

9 I have been asked to provide an update  
10 on the agency's approach to the safety issue of  
11 gadolinium retention after administration of  
12 gadolinium based contrast agents. Let's see if  
13 this ----

14 By way of introduction, here are a few  
15 key facts about the gadolinium based contrast  
16 agents or GBCAs. They are the only approved  
17 class of drugs for use when MRI ---- for use  
18 with MRI in the United States. They are the most  
19 intravenously administered drug class after  
20 saline iodinated contrast agents.

21 They are mainly indicated to detect  
22 and visualize areas with disrupted blood brain

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1 barrier and/or abnormal vascularity of the  
2 central nervous system based on efficacy evidence  
3 that blinded readers report improved  
4 visualization ratings when comparing pre-plus  
5 post-GBCA images to pre-GBCA images alone.

6 And FDA recognizes that off-label use  
7 is common for general anatomical and certain  
8 functional diagnostic information provided by MRI  
9 across body regions.

10 The next slide provides a summary of  
11 the seven GBCAs currently marketed in the United  
12 States. The take home from this busy table is  
13 the communication involving GBCAs is clearest  
14 using trade names.

15 Magnevist, the first GBCA was approved  
16 in 1988 and approval for the foremost recently  
17 marketed agent starting with MultiHance extends  
18 down to term birth. So that's the introduction  
19 to the GBCA drug class.

20 Now, let's talk about the classified  
21 safety issue. A good starting point for the  
22 gadolinium retention story is 1984 with the

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1 publication of the first paper on a GBCA,  
2 excerpts of which are shown on this slide.

3 Starting in the upper left with the  
4 chemical structures, the paper described how  
5 atoms of gadolinium, an element from the  
6 lanthanide row of the periodic table, could be  
7 combined with an organic DTPA chelate to create  
8 the gadolinium DTPA complex, later renamed ----  
9 later named Magnevist, shown in slide center.

10 The innovation here was that the  
11 complex still interacted with local water  
12 molecules to add contrast to MRI images. But,  
13 with less toxicity compared to after injection of  
14 gadolinium alone as shown by the 20x decrease in  
15 rat LD50 values highlighted in the table on the  
16 upper right.

17 Turning to the tables on the bottom,  
18 also notable was that mass balance excretion of  
19 the drug from rats increased from a couple of  
20 percent points after injection of simple  
21 gadolinium highlighted on the left, to excretion  
22 of 97 percent range after injection of chelated

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1 gadolinium highlighted on the right.

2 The latter small gap between almost  
3 100 percent excretion and 100 percent excretion,  
4 which was easy to minimize by comparison to  
5 simple gadolinium is the recurring theme of the  
6 gadolinium retention story.

7 So let's fast forward 15 years. By  
8 1999, Magnevist and two other GBCAs were widely  
9 marketed having received U.S. and international  
10 approval based on studies demonstrating favorable  
11 benefit-risk.

12 Indeed, the class was generally  
13 believed to be safer compared to iodinated  
14 contrast agents for X-ray imaging as illustrated  
15 by this particularly colorful quote from a  
16 publication by a leading GBCA chemist.

17 The successful penetration of  
18 gadolinium chelates can be measured in many ways.

19 The inert complex actually does not look like  
20 much at all. A little hydrophilic ball, as  
21 innocuous as a sugar molecule and oddly enough it  
22 appears to be as safe.

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1           That same year, Shawn Cowper and his  
2 colleagues published their first case series on a  
3 mysterious new disease they called  
4 scleromyxedema-like cutaneous diseases in renal  
5 dialysis patients. Not until seven years later  
6 would this new disease be linked to GBCAs and  
7 renamed nephrogenic system fibrosis or NSF.

8           In 2006, NSF was discovered to be a  
9 serious delayed systemic and chronic rare adverse  
10 Fibrosine reaction to GBCA administration. It  
11 was observed only in patients with renal failure.

12           Unfortunately, incident cases have  
13 declined toward near zero since GBCAs were  
14 contraindicated or relatively contraindicated as  
15 detailed in these current classified black box  
16 warnings finalized in 2010.

17           I wish I could report that our story  
18 drew to a tidy conclusion here almost a decade  
19 ago. But, it didn't. In 2014, a paper was  
20 published out of Japan linking a subtle  
21 MR Imaging finding of increased signal intensity  
22 in the globus pallidus indented nucleus.

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1           The latter shown here to prior GBCA  
2           administration even in patients with normal renal  
3           function. Follow up animal and autopsy studies  
4           have confirmed that this imaging finding is  
5           indeed caused by brain gadolinium retention.

6           The discovery that nanomole per gram  
7           concentrations of gadolinium remain in the brain  
8           after GBCA administrations surprised everyone  
9           for at least two reasons. First, GBCAs were  
10          understood not to cross the intact blood brain  
11          barrier.

12          And second, to the extent gadolinium  
13          was retained anywhere in the body of patients  
14          with normal renal function, the levels were  
15          generally considered to be undetectable outside  
16          of all but the most sophisticated chemistry labs.

17          So, how have we responded to this  
18          surprise? Our focus has been on guiding rapidly  
19          growing research into gadolinium retention toward  
20          one main question. What are the safety  
21          implications?

22          In July 2015, we issued the first of

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1 three drug safety communications to address this  
2 question stating that recent publications have  
3 reported to positive GBCAs remain in the brains  
4 of some patients who undergo four or more  
5 contrast MRI scans. And that it's unknown  
6 whether this is harmful.

7 Last May, after European authorities  
8 announced that marketing authorization might be  
9 withdrawn for certain GBCAs, we provided an  
10 update to the effect that all GBCAs are  
11 associated with the retention in the brain and  
12 other body tissues, but that no available  
13 evidence suggested this was harmful. Restricting  
14 GBCA use was not warranted.

15 Finally, last September we convened an  
16 advisory committee to address public concern  
17 around the safety issue culminating in the  
18 announcement that sensitive safety studies have  
19 potential to build on mostly reassuring evidence  
20 reviewed to date and that a new class warning and  
21 medication guide, human and animal studies, and  
22 enhanced pharmacovigilance were required going

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1 forward.

2 The next slide summarizes the key  
3 messages of the new label warning for clinicians  
4 and medication guide for patients. MRI with a  
5 GBCA helps your doctor to see problems better  
6 than an MRI without a GBCA.

7 GBCAs contain a metal called  
8 gadolinium. Small amounts can stay in your body  
9 including the brain, bone, skin, and other parts  
10 of your body for a long time, several months to  
11 years.

12 It is not known how gadolinium may  
13 affect you, but, so far, studies have not found  
14 harmful effects in patients with normal kidneys.

15 Rarely, patients have reported pains, tiredness  
16 and skin, muscle or bone ailments for a long  
17 time, but these symptoms have not been directly  
18 linked to gadolinium.

19 Gadolinium stays in the body more  
20 after Omniscan or Optimark than after either  
21 Eovist, Magnevist, or MultiHance. Gadolinium  
22 stays in the body the least after Dotarem,

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1 Gadavist, or ProHance.

2 People who get many doses, women who  
3 are pregnant, and young children may be at  
4 increased risk. Consider retention  
5 characteristics when choosing GBCAs for these  
6 patients. Minimize repetitive and closely spaced  
7 administrations.

8 I'd like to conclude by shifting from  
9 a historical perspective to a preview of our  
10 approach to safety evidence generation going  
11 forward. Suffice it here to say that we think of  
12 the sources of evidence to inform our  
13 understanding as falling into descriptive and  
14 analytical categories. And that our focus going  
15 forward is on the bottom two rows.

16 On the generation of perspective  
17 controlled trials primarily designed to exclude a  
18 clinically meaningful magnitude of neural  
19 behavioral harm, both in juvenile animal studies  
20 and matched control cohort trials in  
21 neurologically normal adults. The protocols for  
22 which are under active development.

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1           Finally, given the interest of this  
2 committee, I'd like to conclude with a slide that  
3 focuses on trends in pediatric GBCA use. This  
4 figure was prepared by my colleague, Patty Greene  
5 from our Office of Surveillance in Epidemiology.

6           It shows GBCA sales from manufacturers  
7 to a sample of pediatric hospitals and clinics  
8 and requires a bit more back story regarding the  
9 difference between the red macrocyclic and blue  
10 linear lines.

11           Recall from the beginning of our  
12 retention story timeline that GBCAs are  
13 manufactured by combining gadolinium ions with  
14 organic chelating molecules to promote excretion  
15 and safety.

16           Also recall, that there are two black  
17 box warnings for NSF with slightly different  
18 wording such that MRIs contraindicated for  
19 patients with renal failure only for the three  
20 agents most strongly associated with NSF.

21           The geometry of the organic chelate  
22 for these three agents, Magnevist, Omniscan, and

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1 Optimark is more open chain or linear compared to  
2 the structure of the chelate for ProHance,  
3 Gadavist, and Dotarem, referred to as the closed  
4 chain or macrocyclic GBCAs.

5 In particular, compared to the  
6 macrocyclics, these three linear GBCAs are both  
7 more closely associated with NSF in patients with  
8 renal failure and most retained in all patients,  
9 including patients with normal renal function.

10 This figure suggests a clear shift in  
11 pediatric use from linear to macrocyclic agents  
12 shortly following a period of time when two new  
13 macrocyclic agents were approved including  
14 supplemental approval down to term birth starting  
15 in 2014.

16 In conclusion, available evidence  
17 suggests benefit risk remains favorable for all  
18 GBCAs. However, the stronger association of some  
19 agents with NSF and theoretical concerns based on  
20 relative retention and biochemical properties may  
21 represent factors that stakeholders choose to  
22 focus on when selecting agents from among the

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1 choices on the market. Particularly for  
2 populations more vulnerable to subtle and/or  
3 delayed harm that is challenging to study, such  
4 as pediatric patients. Thank you.

5 DR. DRACKER: Thank you very much for  
6 that presentation.

7 MS. BRILL: Okay, transportation going  
8 back to the hotel, the shuttle will be out in  
9 front of Building 1 at ten minutes before 4:00  
10 o'clock this afternoon.

11 The shuttle can only accommodate, I  
12 believe 10 or 12 people so you have an option of  
13 calling an Uber. So, you can Uber back to the  
14 hotel.

15 Tomorrow morning at 7:30 a.m., the  
16 shuttle will pick you up and then drop you off  
17 here. So, it's 7:30. Please try to wait for  
18 your colleagues.

19 Again, space is limited so you may  
20 Uber coming to the FDA And, if you haven't not  
21 turned in your CDCF, please leave them on your  
22 desk or a on the tables and then we will collect

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1       them. Thank you.

2                   Oh, we will have a training tomorrow  
3 that's going to start at 8:30 a.m. So, they will  
4 go over some labeling regulation and a whole  
5 stuff. Suzie, you want to say something more  
6 about it?

7                   DR. MCCUNE:       This is just an  
8 opportunity for us to go over some aspects of FDA  
9 101 that we've heard today a little bit. We're  
10 going to talk about drug regulations and drug  
11 approval processes, efficacy safety, and then  
12 drug labeling.

13                   So it should be a --- and very  
14 relevant to the conversations that we have had --  
15 - you've had today and that the presentations  
16 that we've heard.

17                   DR. DRACKER:       I want to thank  
18 everyone. I think you've helped the FDA quite a  
19 bit. And I think we appreciate all the hard work  
20 that the FDA does as well. So, thank you Suzie.  
21 Thank all of you.

22                   (Whereupon, the above-entitled matter

1       went off the record at 3:22 p.m.)

2