

UNITED STATES FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Monday, March 6, 2017

1 PARTICIPANTS:

Welcome and Introductory Remarks:

2

MARK HUDAK, MD

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Chair of Pediatric Advisory Committee (PAC)

Assistant Dean of Managed Care for the

4

University of Florida College of Medicine -  
Jacksonville

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Assistant Medical Director

Neonatal Intensive Care Unit

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University of Florida Health Science Center  
Jacksonville, Florida

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Review of Agenda and Introduction of Dr. McCune,  
the New Director of the Office of Pediatric  
Therapeutics:

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ROBERT "SKIP" NELSON, MD, PhD

10

Deputy Director, Office of Pediatric

Therapeutics

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Office of the Commissioner (OC)

Food and Drug Administration

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Opening Statement:

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MARIEANN R. BRILL, MBA, RAC, MT (ASCP)

14

Designed Federal Official, PAC

Office of Pediatric Therapeutics

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Office of the Commissioner (OC)

Food and Drug Administration

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Silver Spring, Maryland

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Pediatric Focused Safety Review Update - Exjade  
(deferasirox):

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PETER WALDRON, MD

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Division of Pharmacovigilance II

Office of Pharmacovigilance and Epidemiology

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Center for Drug Evaluations and Research

(CDER), FDA

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## 1 PARTICIPANTS (CONT'D):

2 KATE GALPERIN, MD, Medical Officer  
3 Division of Epidemiology I  
4 Office of Surveillance and Epidemiology,  
(CDER), FDA

5 Standard Review of Adverse Event Presentation  
6 Kuvan (sapropterina dihydrochloride):

7 JACQUELINE SPAULDING, MD  
8 Division of Pediatric and Maternal Health  
Office of New Drugs, CDER,  
Food and Drug Administration

9 Nitropress (sodium nitroprusside):

10 LILY (YERUK) MULUGETA, Pharma D  
11 Division of Pediatric and Maternal Health  
Office of New Drugs  
12 Food and Drug Administration

13 The Role of Pharmacogenomic Data in  
Pediatric Therapeutics:

14 ROBERT "SKIP" NELSON, MD, PhD  
15 Deputy Director, Office of Pediatric  
Therapeutics  
16 Office of the Commissioner (OC)  
Food and Drug Administration

17 Pharmacogenomics in Pediatric Product  
18 Development and Labeling:

19 DIONNA GREEN, MD  
20 Medical Officer/Policy Lead Guidance  
And Policy Team  
21 Office of Clinical Pharmacology  
Food and Drug Administration

22

1 PARTICIPANTS (CONT'D):

2 Case Studies in Pharmacogenomics:

3 MICHAEL PACANOWSKI, Pharm D, MPH  
4 Office of Office of Clinical Pharmacology  
5 Center for Drug Evaluation and Research  
6 Food and Drug Administration

7 Analytical and Clinical Validation of  
8 Pharmacogenetic Tests:

9 KELLIE B. KELM, PhD  
10 Chief, Cardio-Renal Diagnostic Devices Branch  
11 Division of Chemistry and Toxicology Devices  
12 Office of In Vitro Diagnostic Devices  
13 And Radiological Health  
14 Food and Drug Administration

15 Clinical Implementation of Precision Therapeutics  
16 In Children:

17 J. STEVEN LEEDER, PharmD, PhD  
18 Director, Division of Clinical Pharmacology,  
19 Toxicology and Therapeutic Innovation  
20 Associate Chair-Research  
21 Department of Pediatrics Deputy Director  
22 Children's Research Institute  
23 Children's Mercy Kansas City  
24 Professor of Pediatrics and Pharmacology  
25 UMK Schools of Medicine and Pharmacy

26 Discussion:

27 MARK HUDAK, MD  
28 Chair of Pediatric Advisory Committee

29 Summary and Wrap-up:

30 ROBERT "SKIP" NELSON, MD, PhD  
31 Deputy Director, Office of Pediatric  
32 Therapeutics  
33 Office of the Commissioner (OC)  
34 Food and Drug Administration

1 PARTICIPANTS (CONT'D):

2 Adjournment:

3 MARK HUDAK, MD  
4 Chair of Pediatric Advisory Committee

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## 1 P R O C E E D I N G S

2 (8:30 a.m.)

3 DR. HUDAK: Good morning. I think we'll  
4 get started. It's 8:30. Welcome to the meeting  
5 of the Pediatric Advisory Committee. I'm Mark  
6 Hudak and I have the privilege of chairing this  
7 meeting. So we have a very full and interesting  
8 agenda today as always. A couple of  
9 administrative items we need to do this morning.  
10 But we'll start by going around the table and  
11 having the members around the table introduce  
12 themselves. We have some new members and some new  
13 consultants. So this will be informative for  
14 everybody. So, I guess we'll start with Dr.  
15 Portman. Caught you unaware there. Sorry.

16 DR. PORTMAN: You did. You did indeed.  
17 So I'm Ron Portman. I'm a Pediatric Nephrologist.  
18 And I represent industry, working at the Pediatric  
19 Therapeutic Area of Novartis.

20 DR. TURER: I'm Christy Turer. I am a  
21 combined Internal Medicine Pediatric attending at  
22 UT of Southwestern and the Director of the

1 Academic General Pediatric Scholarship Program.

2 DR. SAYEJ: Good morning. I am Wael  
3 Sayej, Pediatric Gastroenterologist from  
4 Connecticut Children's Medical Center in the  
5 University of Connecticut. I am also the  
6 Fellowship Director of the Pediatric  
7 Gastroenterology fellowship there.

8 DR. KASKEL: Good morning. I'm Rick  
9 Kaskel, Pediatric Nephrologist. I'm at Einstein  
10 Montefiore, Director of Child Health for the CTSA.

11 DR. ANNE: Good morning. I'm Premchand  
12 Anne, Pediatric Cardiologist. I'm at St. John  
13 Hospital and Medical Center in Detroit, Michigan.

14 DR. WADE: Good morning. I'm Kelly  
15 Wade. I'm a Neonatologist at Children's Hospital  
16 of Philadelphia and the University of Pennsylvania  
17 School of Medicine.

18 DR. CATALETTO: My name is Mary  
19 Cataletto. I'm a Pediatric Pulmonologist at  
20 Winthrop University Hospital in New York.

21 MS. MOORE: Good morning. My name's  
22 Erin Moore. I'm a Healthcare Navigation

1 consultant. I have a six year old son who has  
2 cystic fibrosis. And I work at Cincinnati  
3 Children's Hospital on the Cystic Fibrosis  
4 Learning Network. And also, I'm with Eli Lilly  
5 Pharmaceuticals on Clinical Trial Innovation.

6 DR. WHITE: Michael White from New  
7 Orleans. I'm part of the UQ Ochsner Clinical  
8 School, Pediatric Cardiologist.

9 DR. CALLAHAN: I'm David Callahan, I'm a  
10 Child Neurologist, part of Washington University  
11 Physicians in St. Louis.

12 MS. BRILL: I'm Marieann Brill. I'm the  
13 Designated Federal Officer for this meeting.

14 DR. ZUPPA: Hi. I'm Athena Zuppa. I'm  
15 a Pediatric Intensivist and Clinical  
16 Pharmacologist from the Children's Hospital of  
17 Philadelphia.

18 DR. CNAAN: Avital Cnaan. I'm a  
19 Biostatistician, George Washington University,  
20 D.C.

21 DR. COPE: Hi. Judy Cope, Pediatrician,  
22 Epidemiologist. I head up the Safety Team in the



1 Office of Pediatric Therapeutics at FDA.

2 DR. HAUSMAN: Ethan Hausman, CEDR's  
3 Division of Pediatric and Maternal Health.  
4 Pediatrician and Pathologist.

5 DR. NELSON: Skip Nelson. I'm the  
6 Deputy Director of the Office of Pediatric  
7 Therapeutics. Formally in Neonatology and  
8 Pediatric Critical Care.

9 DR. ALEXANDER: My name is John  
10 Alexander. I'm the Deputy Director of the  
11 Division of Pediatric and Maternal Health and the  
12 Center for Drug Evaluation and Research at FDA.

13 MS. WEINEL: Hello.

14 MR. HUDAK: Let me check if there are  
15 two people on the phone.

16 MS. WEINEL: Yes. This is Pam WEINEL.  
17 I'm the Project Manager for this meeting. And  
18 there are two people on the phone. And we're  
19 going to see if they can come in and say hello.

20 DR. KISHNANI: Good morning. This is  
21 Priya Kishnani. I'm a Clinical Advisor  
22 (inaudible).

1 DR. HAVENS: I'm Peter Havens.

2 Pediatrician

3 (inaudible) Infectious Diseases at  
4 the Medical College of Wisconsin  
5 and Children's Hospital of  
6 Wisconsin in Milwaukee. And  
7 there's a lot of feedback on my  
8 phone. I don't know what's going  
9 on.

10 DR. KISHNANI: I caught the same thing.  
11 I have a lot of feedback.

12 MS. WEINEL: We're trying to get the  
13 sound right. So, just wait one minute and we're  
14 going to see if you're --. You're sounding better  
15 in here. Just wait one minute. Is it better?

16 DR. HUDAK: Yes.

17 DR. HAVENS: Yes. Now it's better.

18 DR. KISHNANI: Yes. Yes.

19 MS. WEINEL: Great.

20 DR. HUDAK: Welcome to those on the  
21 phone. And if I forget to call you when it's  
22 voting time for different matters, please speak

1 up. So, now I'll turn it over to Dr. Nelson, who  
2 has some business to take care of.

3 DR. NELSON: Thanks Mark. So before I  
4 review the Agenda, I thought I would introduce  
5 Suzie McCune, who is our new Director of the  
6 Office of Pediatric Therapeutics. Susie can --  
7 she likes short introductions. But let me just  
8 say, Suzie's been around at the agency probably  
9 for, I don't know,

10 15 years. She started, I believe, in  
11 the Office of Pediatrics and Counterterrorism,  
12 back in the days they called it Babes and Bombs,  
13 before the Office of Pediatric Therapeutics was  
14 founded, which was -- the OPT was founded in, I  
15 think, 2002. So, I don't know if Suzie -- Suzie's  
16 a Neonatologist by the way. And was at Children's  
17 National Medical Center before joining FDA. So do  
18 you want to just say hello Suzie, or is that --?

19 DR. MCCUNE: Hello.

20 DR. NELSON: (Laughter)

21 DR. MCCUNE: Skip told me that's all I  
22 have to say, so. So, I just want to thank you all

1 for coming today. And I'm looking forward to the  
2 discussion and it's really nice to be part of this  
3 group (inaudible).

4 DR. NELSON: It's actually -- Suzie  
5 reminded me, I think she actually presented some  
6 of the safety stuff to the Committee back in 2003  
7 and 2004. Somewhere around that range. So, life  
8 circles back around. Well anyway, so let me  
9 review the Agenda briefly for you. As you see,  
10 the first thing that's after the open public  
11 hearing is the Pediatric Focus Safety Review  
12 update on Exjade or deferasirox. I think I'm  
13 pronouncing that correctly. And as you know, this  
14 arose out of a -- a review, a couple of meetings  
15 ago now. I suspect a year. Could have been a  
16 year and a half. This is going to be a fairly  
17 substantive update. Though the review is not  
18 complete. So, presumably there'll be another  
19 update after that. But I suspect the -- that  
20 further one would a bit more focused.

21 And then, you'll have two standard  
22 reviews. As you know, we're now going through a

1 process that we had described and implemented over  
2 the past year of going to web posting for items  
3 that are low risk. So the materials that had  
4 previously come in abbreviated reviews, are now  
5 going directly to the web for review and comment.  
6 And so you see that reflected in the agenda within  
7 the CDER products, being less in numbers. But  
8 hopefully more robust in terms of the issues that  
9 can be discussed with each product. Then, we  
10 spend the afternoon talking about  
11 pharmacogenomics. You may recall there was a  
12 discussion that was stimulated by a (inaudible)  
13 last time about the role of pharmacogenomic  
14 information in labeling. And we had talked about  
15 having a discussion of that topic. So this is  
16 that discussion. We can talk a bit more about  
17 that after lunch. But we're looking forward to  
18 that conversation. And then, I think I can  
19 introduce tomorrow's agenda tomorrow. So, with  
20 that Mark, I'll give it back to you.

21 DR. HUDAK: Very good. Okay. So we are  
22 already ahead of time. A longer lunch for

1       everybody perhaps. All right, so -- so Ms. Brill,  
2       for the opening statement.

3                   MS. BRILL: Okay. The following  
4       announcement addresses the issues of conflict of  
5       interest with regards to today's discussion of  
6       reports by the agency as mandated by the Best  
7       Pharmaceuticals for Children Act and Pediatric  
8       Research Equity Act. With the exception of the  
9       industry representative, all participants of the  
10      Committee are special government employees or  
11      regular federal employees from other agencies that  
12      are subject to the Federal Conflict of Interest  
13      Laws and Regulation. The following information on  
14      the status of the Advisory Committee's compliance  
15      with the Federal Conflict of Interest Laws,  
16      including, but not limited to 18 U.S.C., Section  
17      208 of the Federal Food Drug and Cosmetic Act, is  
18      being provided to participants at this meeting and  
19      to the public. FDA has determined that members of  
20      the Advisory Committee are in compliance with  
21      Federal Ethics and Conflict of Interest Laws. As  
22      Dr. Nelson had alluded a while ago, today's Agenda

1 will include pediatric focus safety reviews for  
2 Kuvan and Nitropress. The FDA will also provide  
3 analysis regarding the use of the drug product  
4 Exjade. In order to provide the expertise  
5 required to adequately (Coughs) to adequately  
6 address all of the products covered at today's  
7 meeting, the following expert consultants will be  
8 participating as temporary voting members. Dr.  
9 Anne, Dr. Kaskel, Dr. Callahan, Dr. Zuppa and Dr.  
10 Kishnani. Ms. Erin Moore is participating as the  
11 patient family representative, which is a voting  
12 position. Dr. Brigitte Jones will serve as a  
13 Pediatric Health Organization representative,  
14 which is a non-voting position. Dr. Portman is  
15 participating in this meeting as the industry  
16 representative acting on behalf of all related  
17 industry. He is employed by Novartis  
18 Pharmaceuticals Corporation. Dr. Portman is not a  
19 special government employee and does not vote.

20 There is one waiver that was issued for  
21 this meeting. Under 18 U.S.C., 208 B3, Dr. Leeder  
22 has been granted a waiver to participate in the

1 discussion of Strattera during the pharmacogenomic  
2 session this afternoon. The information regarding  
3 his waiver is available in the Pediatric Advisory  
4 Committee website. As a guest speaker, Dr. Leeder  
5 will not participate in committee deliberations,  
6 nor will he vote. We would like to remind members  
7 and temporary voting members, that if discussions  
8 involve any other products or firms not already on  
9 the agenda, for which an FDA participant has a  
10 personal or imputed financial interest, the  
11 participants need to exclude themselves from such  
12 involvement. The exclusion will be noted for the  
13 record.

14 FDA encourages all other participants to  
15 advise the Committee of any financial  
16 relationships that you may have with the firms  
17 that could be affected by the Committee  
18 discussions. I'd like to remind the audience that  
19 the final version of the agenda and the materials  
20 that will be posted of today's meeting, I'm sorry,  
21 that will be presented at today's meeting, will be  
22 posted on the Pediatric Advisory Committee



1 website. So, any copies of slides that you have  
2 that appear different from the ones that are on  
3 the screen, will be updated. For the members of  
4 the Committee and those around the table, the  
5 meeting is being transcribed. And as such, when  
6 you are acknowledged to make a statement, or have  
7 a question, please press the button on your  
8 microphone and state your name prior to beginning  
9 your statement. I also request all meeting  
10 attendees to turn their electronic devices to  
11 silent mode. Thank you.

12 DR. HUDAK: Okay. We are now open for  
13 --. Yes Dr. Portman?

14 DR. PORTMAN: I just want to make sure  
15 that it's clear that while I'm -- I'm non-voting  
16 anyway, but I'm -- Exjade is a Novartis product,  
17 so I won't participate in that discussion.

18 DR. HUDAK: Okay. Thank you. Okay. We  
19 are now at the part of the meeting where we have  
20 an open public session. We did not have anybody  
21 sign in for this. But of course, anybody -- is  
22 anybody in the audience here to make an opening

1 statement? Okay. Well then --. Hmm?

2 MS. BRILL: They cancelled last  
3 (inaudible).

4 DR. HUDAK: They cancelled?

5 MS. BRILL: Yes.

6 DR. HUDAK: So we will --

7 MS. BRILL: One cancelled. One didn't.

8 DR. HUDAK: -- we have opened and we  
9 will now close the open -- yes Skip.

10 DR. NELSON: Yeah. We -- we can go  
11 ahead and do that, but in case someone shows up at  
12 9 o'clock, thinking it's

13 o'clock, we should just make sure, since  
14 we're 15 minutes early. But we can certainly move  
15 ahead with the agenda, but we'll -- at 9 o'clock,  
16 maybe double check that no one walked in thinking  
17 that they had an opportunity. But, that's fine.

18 DR. HUDAK: Perfect. Okay. All right.  
19 So, with that in mind, we will begin the  
20 discussion on Exjade. And as members -- some  
21 members of the committee will remember, we did  
22 have a public hearing in 2015, I believe, where

1       there was some concern raised by one parent and by  
2       the -- I think the President of the Cooley's  
3       Anemia Association regarding concerns with respect  
4       to fever and potential adverse effects on Exjade.  
5       So the Committee at that time recommended to the  
6       FDA to go back and conduct further investigation  
7       on this issue. And today we have a presentation  
8       that begins to address some of these questions.  
9       And I'm not sure who is speaking first. We have  
10      Dr. Waldron and Dr. Gelperin to present some  
11      information. So, it looks like Dr. Waldron is up.  
12      So if you could sort of briefly in introduce  
13      yourself and -- and get on to your presentation.

14                 DR. WALDRON: Okay. My name is Peter  
15      Waldron. I'm a Pediatric Hematologist Oncologist.  
16      I don't know whether you have my biography or I  
17      should do that myself. Okay. Let's see. I was a  
18      -- on the faculty of the University of Virginia.  
19      On Pediatric Hematology Oncology. My focus was on  
20      non-malignant hematology. I was there from 1990  
21      to 2010. And then I joined the Food and Drug  
22      Administration in the Office of Surveillance and

1 Epidemiology, in the Division of Pharmacovigilance  
2 with the focus on hematology oncology products.  
3 So, today Dr. Kate Gelperin and I will be  
4 presenting the findings from the focus review on  
5 deferasirox. Also known by the trade names Jadenu  
6 and Exjade. Exjade is the most commonly used term  
7 and that's the one I will likely use. So, just  
8 for some background, this request followed the  
9 presentation of a pediatric focus review in  
10 September 2015 of deferasirox. During that  
11 meeting, a statement was made by a parent  
12 regarding the unexpected death of her almost three  
13 year old child in association with the use of  
14 Exjade. And, at the same meeting, a request was  
15 made by the Cooley's Anemia Foundation, which is a  
16 thalassemia focused disease organization. For the  
17 FDA to make a recommendation about whether to  
18 interrupt deferasirox if a child develops a fever.  
19 So in response to this request, we did an initial  
20 survey of material and we concluded that fever was  
21 common among children in general. And among the  
22 children who participated in the deferasirox

1 clinical trials. However, the analysis of the  
2 febrile events among those sources did not  
3 attribute any adverse events to fever. We then  
4 reviewed the initial case, the product information  
5 and the literature, and concluded that dehydration  
6 or hypovolemia, which is a common feature of acute  
7 pediatric illnesses and may occur independently  
8 from febrile illnesses, should be an additional  
9 focus of our review of this drug, which is labeled  
10 for nephrotoxicity. A principal source to answer  
11 the Committee's question is FAERS data. That's  
12 the FDA Adverse Event Reporting System. We were  
13 concerned that FAERS data and comparisons of FAERS  
14 data, I'm sorry, of FAERS cases, that continued to  
15 or interrupted deferasirox use during acute  
16 illnesses may not provide robust answers for this  
17 request. So, we engaged our Office of  
18 Surveillance and Epidemiology colleagues in the  
19 Division of Epidemiology, to examine clinical  
20 trial sources that may provide a clearer answer.  
21 The identification acquisition of appropriate  
22 clinical trial data was a prolonged process before

1 the first step of analysis could be done.  
2 However, we do feel that the Division of  
3 Epidemiology's effort met the goal of a more  
4 robust data set and analysis to provide rigor to  
5 an answer to the Advisory Committee's request.  
6 Dr. Kate Gelperin will present that summary. Also  
7 in reviewing the data at the beginning, it became  
8 clear that the information relative to pediatric  
9 risks and modifications regarding renal adverse  
10 effects, may benefit from a review. Dr. Mona  
11 Khurana, who is a Pediatric Nephrologist in the  
12 Division of Pediatric Maternal Health, were  
13 consulted to review those issues and to advise the  
14 team on Nephrology questions. I'll refer to that  
15 review only briefly. Last, I will describe  
16 additional ongoing safety evaluations for the use  
17 of deferasirox in children. The data sources that  
18 we used are listed on the slide. They include  
19 post-marketing reports from FAERS. Published  
20 literature and clinical trial in pharmacology data  
21 submitted to the FDA by the sponsor Novartis.

22 The FAERS analysis. The Safety

1 Evaluators, Dr. Page Crew and Sahart  
2 Patanavanich, sorry, of the DPV, completed the  
3 analysis of the FAERS database, to detect renal  
4 and hepatic impairment following the occurrence of  
5 fever and/or dehydration among pediatric patients  
6 on deferasirox therapy. For inclusion, they  
7 searched the FAERS database, using fever and  
8 dehydration related preferred terms for pediatric  
9 patient's ages 2 to 15 years old, with deferasirox  
10 as the suspect product. They excluded any  
11 duplicate cases, as well as patients with sickle  
12 cell disease, which we determined to be a possible  
13 confounding factor because of the high frequency  
14 of disease related renal and hepatic impairment  
15 among that population. Also excluded were cases  
16 where the FAERS report did not support fever or  
17 dehydration or had insufficient information for  
18 further assessment. Upon reviewing the  
19 narratives, if a patient had multiple episodes of  
20 fever or dehydration within a report, all of the  
21 episodes of fever or dehydration were noted. In  
22 our analysis of these reports, we evaluated the

1 disposition of deferasirox therapy at the time of  
2 fever or dehydration, as a possible risk factor  
3 for subsequent serious adverse events. The  
4 disposition was classified as continue, based on  
5 the intent to treat model, where if the patient  
6 received at least one dose of deferasirox therapy,  
7 after onset of the fever or dehydration episode,  
8 then that patient would be counted as being a  
9 continue on therapy patient. Or, I should say,  
10 the event accounted that way. The patient is  
11 considered to have discontinued therapy, if the  
12 narrative described stopping therapy on the first  
13 day of fever or dehydration, regardless of whether  
14 it was self-initiated or at the direction of a  
15 provider. The disposition is noted as unknown if  
16 the disposition of deferasirox therapy was not  
17 stated clearly in the report.

18 Patients with known disposition of  
19 deferasirox therapy were then analyzed in three  
20 sub-groups. A fever only, dehydration only and  
21 those with concurrent fever and dehydration. We  
22 then evaluated these cases (Coughs) excuse me, for



1 subsequent renal or hepatic impairment within  
2 seven days prior to fever or dehydration events.  
3 Or, within 28 days after the onset of a fever  
4 and/or dehydration event, to allow for some  
5 expected temporal discrepancies in spontaneous  
6 reports.

7 (Coughs) Excuse me. Our FAERS  
8 search identified 183 episodes of  
9 fever or dehydration. We were able  
10 to determine the disposition of  
11 deferasirox therapy, which means  
12 continue or discontinue, in 149 of  
13 the episodes. Breaking down into  
14 sub- groups, there were 58 fever  
15 only episodes. 69 dehydration only  
16 episodes. And 23 episodes of  
17 concurrent fever or dehydration.  
18 Hopefully that's clear in the  
19 algorithm here. Okay.

20 So, among the fever only cases, or  
21 episodes, there were almost 12 percent. 11.8  
22 percent were roughly 1/9 of patients who continued

1 therapy in association with the fever episodes,  
2 reported subsequent renal impairment compared to  
3 33 percent or 1/3 frequency of renal or hepatic  
4 impairment among patients who discontinued. So  
5 the discontinued patients then had a higher  
6 frequency of hepatic or renal adverse events  
7 compared to the patients with fever only who  
8 continued. Among the dehydration only episodes,  
9 for the 68 episodes in this sub- group, we also  
10 observed the patients who discontinued deferasirox  
11 therapy, reported a higher number of renal and/or  
12 hepatic impairment, compared to those who  
13 continued therapy. Approximately 50 percent or  
14 half of the discontinued group versus 30 percent  
15 in the continued group. We also noted that taken  
16 as a whole, regardless of drug disposition, the  
17 proportion of dehydration episodes with associated  
18 renal or hepatic impairment, which was 42 percent,  
19 was greater than the proportion in the fever only  
20 group, which was 21 percent. In the group who had  
21 both fever and dehydration, we again similarly  
22 observed more reports of renal or hepatic

1       impairment, in patients who discontinued  
2       deferasirox therapy, compared to those who  
3       continued deferasirox. We also observed  
4       proportionately more reports of renal or hepatic  
5       impairments overall, when compared to the fever  
6       only or the dehydration only sub-groups. And now,  
7       some important limitations. There are several to  
8       consider when interpreting the data presented in  
9       the FAERS analysis. Our data source relied  
10      exclusively upon FAERS reports, which are often  
11      limited by incomplete information. In addition,  
12      the results of the FAERS analysis cannot be  
13      interpreted as incidents rates due to the lack of  
14      a reliable denominator. These results from FAERS  
15      cannot be compared with data from clinical trials.  
16      Although the FAERS database is a database of  
17      spontaneously generated reports, we observed that  
18      many patients were involved in active  
19      surveillance, either as a clinical trial or in a  
20      patient assistance program. These reports differ  
21      from spontaneous reports, but we are not able to  
22      say in which way the -- these reports differ. Or,

1        what impact that has on the data. In addition,  
2        there are likely differences between the two  
3        patient populations that comprised the continue  
4        and discontinue groups. The groups may have  
5        different historical and contemporary risks for  
6        adverse events. But these differences may not be  
7        apparent due to incomplete reporting. Also, we  
8        are unable to determine why patients discontinued  
9        deferasirox. Was it in response to identification  
10       for fever or dehydration? Or, was it in response  
11       to an identified renal or hepatic dysfunction?  
12       Although more renal and hepatic impairments were  
13       observed among patients who discontinued  
14       deferasirox. Limited information from FAERS  
15       hampers our ability to fully assess whether the  
16       patients in the discontinue group were more  
17       severely ill compared to those in the continued  
18       deferasirox group. This can potentially lead to  
19       channeling bias. That is, cases in which  
20       deferasirox was continued, may have been selected  
21       for discontinuation based on a poor clinical  
22       status. Finally, our data may be affected by

1 misclassification bias. Due to the limited  
2 information within FAERS reports, there is some  
3 inherent uncertainty regarding the precise timing  
4 of the fever or dehydration episode relative to  
5 deferasirox discontinuation. Further, the  
6 continue group was defined as an intent to treat  
7 approach. Sorry, on an intent to treat approach.  
8 Where approximately 1/3 of patients reported  
9 missing doses. Therefore, there is variability in  
10 deferasirox exposure within that group. Finally,  
11 the half-life of deferasirox is between eight and  
12 sixteen hours, as reported in the product  
13 information. This is in a patient with normal  
14 organ function. Therefore, even after a patient  
15 discontinues deferasirox, they continued to have  
16 systemic drug exposure for approximately 40 to 80  
17 hours, or five half-lives following the last dose.  
18 This period of exposure and the tissue  
19 concentration exposure, may be increased in the  
20 setting of renal and/or hepatic impairment. In  
21 review of case reports in the published  
22 literature, case series and clinical trial data,

1 we found no reports that attributed specific  
2 adverse events to fever. Since the 35 month old  
3 child with a fatal outcome was diagnosed with  
4 respiratory syncytial virus. We searched for an  
5 association between RSV and hepatic or renal  
6 failure. We did not identify any similar cases.  
7 We searched for reports of renal adverse events,  
8 which could be attributed to dehydration. While  
9 we identified some reports, they were confounded  
10 by prior or concomitant medications, which also  
11 have a risk for nephrotoxicity. Our literature  
12 search identified these additional issues, sorry,  
13 additional issues that are listed here, which will  
14 be discussed later. So, the analysis in summary  
15 of the FAERS cases and literature reports, due to  
16 the limitations described, the FAERS data alone is  
17 not a reliable tool for determining effects of  
18 deferasirox continuation or discontinuation among  
19 the fever and dehydration groups on subsequent  
20 renal or hepatic outcomes. A review of the  
21 literature did not identify evidence. The fever  
22 or dehydration are indicators of subsequent

1 increased risk of adverse events. And due to the  
2 limitations in measuring hypovolemia, and  
3 therefore, in detecting and reporting it, we  
4 cannot exclude that hypovolemia increases the risk  
5 for renal or hepatic adverse events. Dr. Kate  
6 Gelperin will present an analysis now of clinical  
7 trial data. She's from the Division of  
8 Epidemiology. This advances the slides forward.  
9 This just goes backwards. This is the laser  
10 pointer.

11 DR. GELPERIN: Thanks Peter. Good  
12 morning. My name is Kate Gelperin and I'm a  
13 Medical Officer and Epidemiologist in the CDER  
14 Office of Surveillance and Epidemiology. During  
15 the next few minutes, I'll be telling you about an  
16 analysis we conducted of clinical trial data.  
17 That's randomized clinical trial data as distinct  
18 from the FAERS data that Dr. Waldron just  
19 described. To evaluate whether signs or symptoms  
20 of fever or dehydration may be useful indicators  
21 for deferasirox treatment interruption to prevent  
22 acute liver or kidney injury in children taking

1 this drug. I'd like to acknowledge the  
2 contributions of Sara Kurami and the Data  
3 Management and Analysis team. And Yung Ma in the  
4 Division of Biostatistic 7 for their work on the  
5 data analysis I'll be presenting this morning.  
6 Study 107, the pivotal study on which the original  
7 approval of Exjade was based, is a randomized  
8 comparative open label Phase III trial of the  
9 efficacy and safety of long term treatment with  
10 deferasirox, compared to Diferoxamine and beta-  
11 thalassemia patients with transfusional  
12 hemosiderosis. Data sets identifying fever and  
13 dehydration adverse events in children, ages 2 to  
14 15 years of age, participating in Exjade clinical  
15 trials, were submitted by Novartis at the request  
16 of FDA. The sponsor's submission included  
17 demography, dose and clinical and laboratory  
18 safety data. Our analysis included study subjects  
19 with fever or dehydration adverse events, who  
20 received deferasirox during the randomized or the  
21 extension phase of the study. The analysis data  
22 set for Study 107 was extracted from the larger



1 data set and comprised adequate laboratory data to  
2 evaluate 237 fever adverse events and 126  
3 dehydration adverse events in 273 pediatric  
4 patients from Study 107. The proportion of fever  
5 adverse events and the proportion of dehydration  
6 adverse events with laboratory evidence of liver  
7 or kidney injury, and the distribution of action  
8 taken, that means interruption or adjustment  
9 compared to continuation of deferasirox therapy.  
10 Or assessed across the pre-specified criteria  
11 levels for the laboratory parameters. We also  
12 examined the proportion of fever adverse events  
13 and the proportion of dehydration adverse events  
14 with evidence of liver injury or kidney injury,  
15 after interruption or continuation of deferasirox  
16 therapy among patients whose ALT, alanine  
17 aminotransferase or serum creatinine values had  
18 been within normal limits prior to the adverse  
19 event. And those were the results tables I'll be  
20 discussing in the next four slides.

21 This table shows the proportion of fever  
22 adverse events with transaminase elevations above

1 the upper limit of normal, after continuation or  
2 interruption of deferasirox therapy in the subset  
3 of events, where the ALT, alanine  
4 aminotransferase, was within normal limits prior  
5 to the adverse event. Overall, 17 percent of 157  
6 adverse events in 107 unique pediatric patients  
7 with fever, were followed by some evidence of  
8 liver injury. Transaminases were elevated after  
9 13 percent of fever events, when the study drug  
10 was adjusted. Or -- and  
11 percent when it was not. This table  
12 shows the proportion of dehydration adverse events  
13 with transaminase elevations above the upper limit  
14 of normal, after continuation or interruption of  
15 deferasirox therapy in the subset of events where  
16 the ALT was within normal limits prior to the  
17 adverse event. Overall,  
18 percent of 91 adverse events in 73  
19 unique pediatric patients with signs or symptoms  
20 of dehydration, were followed by some evidence of  
21 liver injury. The proportion of events with  
22 transaminase elevations appears similar whether a

1 drug -- study drug was adjusted or not in this  
2 analysis.

3           This table shows the proportion of fever  
4 adverse events with clinical laboratory evidence  
5 of new or worsening kidney injury after  
6 continuation or interruption of deferasirox  
7 therapy, where serum creatinine was within normal  
8 limits prior to the adverse event. Overall, more  
9 than half, 53 percent of 232 adverse events in 107  
10 unique pediatric patients with fever, were  
11 followed by an increase in serum creatinine of at  
12 least 25 percent. Or an increase in the urine  
13 protein to creatinine ratio. And seven percent of  
14 these fever adverse events were followed by serum  
15 creatinine greater than the upper limit of normal.  
16 Or a markedly abnormal urine protein to creatinine  
17 ratio, greater than 0.6. Although the proportions  
18 of events followed by evidence of kidney injury  
19 were similar, regardless of whether deferasirox  
20 therapy was continued or interrupted due to the  
21 fever adverse event, it should be noted that this  
22 level of kidney injury is in the range where the

1 current labeling for deferasirox mentions dose  
2 adjustment or interruption.

3           This table shows the proportion of  
4 dehydration adverse events with clinical  
5 laboratory evidence of new or worsening kidney  
6 injury, after continuation or interruption of  
7 deferasirox therapy, where the serum creatinine  
8 was within normal limits prior to the adverse  
9 event. Overall, again, 50 percent of 116 adverse  
10 events in 73 unique pediatric patients, with signs  
11 or symptoms of dehydration, were followed by an  
12 increase of serum creatinine of at least 25  
13 percent. Or, an increase in the urine protein to  
14 creatinine ratio. Of note, nine dehydration  
15 adverse events in eight unique patients, were  
16 followed by serum creatinine greater than the  
17 upper limit of normal. Or, a markedly abnormal  
18 urine protein to creatinine ratio greater than  
19 0.6, when deferasirox therapy was continued.  
20 These nine dehydration adverse events were  
21 identified as diarrhea in each case. A similar  
22 injury pattern was not observed in the small

1 number of dehydration adverse events, where  
2 deferasirox therapy was interrupted or adjusted.  
3 Overall, this analysis showed that evidence of  
4 liver or kidney injury was observed commonly in  
5 Study 107 after pediatric fever or dehydration  
6 adverse events. Regardless of whether or not  
7 deferasirox dose was interrupted or adjusted. We  
8 observed that children with signs or symptoms of  
9 fever or dehydration, often developed clinical  
10 laboratory abnormalities of serum creatinine or  
11 urine protein to creatinine ratio in the range for  
12 which dose reduction or interruption are  
13 recommended in the current deferasirox labeling.  
14 Of note, serum creatinine greater than the upper  
15 limit of normal, or markedly abnormal urine  
16 protein to creatinine ratio greater than or equal  
17 to 0.6, were observed in eight subjects with  
18 previously normal serum creatinine when  
19 deferasirox therapy was continued during a  
20 dehydration adverse event. Diarrhea in each case.  
21 A similar injury pattern was not observed in the  
22 small number of dehydration adverse events, where

1        deferasirox therapy was interrupted or adjusted.  
2        I'll turn the podium back to Dr. Waldron for  
3        concluding remarks.

4                    DR. WALDRON:  So in summary, the  
5        clinical trials analysis found following  
6        dehydration or fever events, clinical trial  
7        subjects frequently had lab values for creatinine  
8        or urine protein to creatinine ratio, which were  
9        in the range, that the current deferasirox label  
10       used -- uses to indicate dose reduction or  
11       interruption treatment.  The FAERS analysis with  
12       regard to interruption or continuation of  
13       deferasirox during fever or dehydration adverse  
14       events, did not provide meaningful information for  
15       regulatory action.  And from the medical  
16       literature, we identified no case reports of  
17       children receiving deferasirox, for which we could  
18       attribute a causal role to fever, RSV, or  
19       dehydration in the development of serious adverse  
20       events.  Earlier I mentioned a review by Pediatric  
21       Nephrology, Dr. Mona Khurana and the Division of  
22       Pediatric Maternal Health.  They used the renal

1 findings that were reported from pre-marketing and  
2 post-marketing FDA reviews of Exjade, as their  
3 source material to evaluate whether there are  
4 opportunities to enhance deferasirox safety in  
5 patients as young as two years of age, with fever,  
6 dehydration or both. The Division of Pediatric  
7 Maternal Health made a number of recommendations  
8 to improve communication in the product  
9 information, with regard to the use of deferasirox  
10 in children who are known to have compromised  
11 renal function. In addition, they concluded that  
12 children who have fever with dehydration, or  
13 dehydration alone, may have an increased risk for  
14 renal toxicity, if deferasirox is continued.  
15 Accordingly, they recommended temporary  
16 discontinuation of deferasirox in the presence,  
17 sorry, in the presence of clinical and/or  
18 laboratory evidence of dehydration. We have  
19 ongoing concerns about the safe use of deferasirox  
20 in young children. Deferasirox is a highly potent  
21 chelator. And it requires very careful monitoring  
22 to use it safely. This is reflected in the box

1 warning for hepatic toxicity, renal toxicity and  
2 in the guidelines for monthly, and in some cases,  
3 more frequent laboratory monitoring. The analysis  
4 of study, C1CL670A0107, showed the following fever  
5 or dehydration events subjects frequently had,  
6 sorry, the following fever or dehydration events  
7 subjects frequently had, lab values for creatinine  
8 or urine protein to creatinine ratio, which were  
9 in the range that the current deferasirox label  
10 uses to indicate dose reduction or interruption  
11 treatment. FDA has received case reports of  
12 serious and fatal liver and kidney failure in  
13 young children, taking deferasirox, including the  
14 index case. Several with elevated ammonia levels  
15 and -- and they have been described. Or, they  
16 have been described in those reports. And so we  
17 continue to probe whether predictors of toxicity  
18 can be better characterized and mitigated,  
19 especially in young children. This slide  
20 summarizes our continuing efforts on this -- on  
21 this concern. For hyperammonemia, we are  
22 evaluating 14 cases from FAERS. These cases



1 included patients with hepatic injury and failure,  
2 renal injury and failure and encephalopathy. The  
3 majority of children were ages 2 to 6. Three  
4 cases, including the initially presented case, had  
5 a fatal outcome. We were also reviewing the  
6 clinical trial safety data of the experience of  
7 children ages 2 to 6 years, who received  
8 deferasirox doses greater than 30 milligrams per  
9 kilogram per day. And, the experience of children  
10 who received doses of deferasirox greater than 25  
11 milligrams per kilogram per day, in the context of  
12 a serum ferritin as a measure of body iron burden,  
13 which showed a trend that was decreasing and was  
14 less than 1,000 micrograms per liter.

15           The deferasirox sponsor submitted data  
16 from a pediatric registry trial in January of  
17 2016. The name of the trial is as described in  
18 the third bullet, a Five-Year Observational Study  
19 Registry of children ages 2 to less than 6 at  
20 enrollment, with transfusional hemosiderosis  
21 treated with deferasirox. Those data are under  
22 review. And last, the Pediatric Nephrology review

1 found, as I described, just a short bit ago, that  
2 it was appropriate to assume that clinical  
3 pharmacology of Exjade in adults and pediatric  
4 patients with renal impairment, should be the  
5 same. So that's an appropriate extrapolation.  
6 However, they considered it inappropriate to  
7 extrapolate that the renal toxicity resulting from  
8 increased Exjade exposure in the setting of renal  
9 impairment, is the same in children as it is in  
10 adults. They recommend additional studies for the  
11 renal impaired pediatric population.

12           And then last, recent studies have  
13 raised concerns about the predictability of dose  
14 exposure relationship. These are published  
15 studies that are cited in the background  
16 information. Other studies identified  
17 pharmacogenomic markers that you'll be hearing,  
18 not specifically about these, but that general  
19 topic this afternoon. These markers that are  
20 predictive of serum creatinine elevation, hepatic  
21 enzyme elevation, pharmacokinetics and efficacy.  
22 The Division of Pharmacology sent a -- an

1 information request regarding these topics to the  
2 sponsor to elucidate these issues. So in  
3 concluding measures to assure the safe use of  
4 deferasirox in children, are being actively  
5 evaluated by both the FDA and the sponsor. Once  
6 FDA's safety review is complete, we may determine  
7 that an update to deferasirox labeling is needed.  
8 If so, FDA will work with a sponsor to facilitate  
9 labeling modifications. Thank you for your  
10 attention.

11 MR. HUDAK: Thank you Dr. Waldron and  
12 Dr. Gelperin. That was actually a lot more  
13 informative and a lot more information than --  
14 than I had thought that you might be able to come  
15 up with in a short amount of time. But very good.  
16 Before we open for discussion and comment, just  
17 two bookkeeping items. One, Dr. Jones came in  
18 late. Would you like to say hi?

19 DR. JONES: Hello. Brigitte Jones. I'm  
20 the Pediatric Healthcare representative from the  
21 AAP.

22 DR. HUDAK: And just to close the issue

1 of the open public hearings, nobody has  
2 registered. But, if there's anybody in the  
3 audience who showed up to make a comment at the  
4 o'clock hearing, please announce  
5 yourselves. And if not, we will, I guess,  
6 officially close the public hearing component.  
7 So, we can move on to a discussion of this  
8 information. So the floor is open.

9 DR. NELSON: And since we've had a  
10 number of other people from the FDA join the  
11 table, perhaps they could introduce themselves  
12 too.

13 DR. HUDAK: Oh sure. We have one, two,  
14 three, four people. Okay. Go, you should go  
15 ahead.

16 DR. JONES: Hello, I'm Christopher  
17 Jones, Division Director, Division of  
18 Pharmacovigilance II.

19 DR. PATANAVANICH: Saharat  
20 Patanavanich. Safety Evaluator, Division of  
21 Pharmacovigilance II.

22 DR. CREW: Page Crew, Safety Evaluator,

1 Division of Pharmacovigilance II.

2 DR. ROBIE SUH: Kathy Robie Suh, Clinical  
3 Team Lead Division of Hematology Products in CDER.

4 DR. KASKEL: I have a few questions on  
5 the renal outcomes. Were there any data being  
6 gathered for long term outcome to see if there's  
7 resolution of the signals for the creatinine  
8 elevation and the protein creatinine? Or, also,  
9 blood pressure data on some of these children?  
10 Were there any other markers of injury going on?  
11 You said there were exposures previously in some  
12 of them from potential nephrotoxins. And,  
13 basically, are studies being considered to look at  
14 other biomarkers of early injury for those at risk  
15 from this agent? Such as some of the clinical  
16 tools available now for NGAL measurements in urine  
17 and blood?

18 MR. HUDAK: So, let me just say, that  
19 was a question from Dr. Kaskel. And if anybody  
20 who speaks, could just introduce yourself by name  
21 when you make a comment, so it can go in the  
22 record. Thank you.

1 DR. GELPERIN: It's Kate Gelperin.  
2 Thank you for that question. As Dr. Waldron  
3 mentioned, Novartis has submitted a -- the  
4 results, a full clinical study report for a  
5 Five-Year Pediatric Registry, so it is five years  
6 of longitudinal information on pediatric patients  
7 who were age 2 to 6 years old at the time of study  
8 entry. That is currently under review. And,  
9 actually one of the things that we're particularly  
10 interested in, is the type of markers. And -- and  
11 unfortunately, we're still working with Novartis  
12 to try to identify that kind of information in  
13 what should be a very rich data set, but we're  
14 struggling a little bit to -- to get our hands on  
15 that. So, but that should be a rich data source  
16 and we're, you know, we're still working on that.

17 DR. WALDRON: I'd like to ask you a  
18 question with regard to biomarkers. You know,  
19 that would be a long process of identifying a  
20 hypothesis validating the marker. And then,  
21 agreeing that that would be new safety information  
22 that might be informative. And so that would be a

1 long process. We're certainly, open to those  
2 possibilities. But we're not far down that road  
3 at all.

4 DR. HUDAK: I think Dr. Cnaan had a  
5 question.

6 DR. CNAAN: Yes. This was -- first of  
7 all, thank you. This was really a lot of  
8 excellent information. The question that I have  
9 is, there was no comparison anywhere, especially  
10 in the clinical trial data, to the rate of renal  
11 or liver injury in those clinical trial  
12 participants that did not have any episode of  
13 fever or dehydration. That would be sort of the  
14 background rate to compare what we're seeing. So,  
15 I would appreciate that at the next update, if we  
16 could have that for the clinical trial data.  
17 Also, I'm very pleased that you're looking at  
18 predictability of exposure. It seems that in this  
19 age range, you also may want to look at age itself  
20 a little bit more exquisitely, because it seems  
21 that it really changes from the very young to just  
22 young, so while looking at predictability of

1 exposure, I'd also look at age itself. Another  
2 thing that wasn't clear to me, is that the  
3 formulation somehow changed or the dosing changed.  
4 There were two brand names involved. And I'm not  
5 sure if this is combined data of everything of the  
6 old one, of the new one. If there could be some  
7 clarification of that. And certainly, in the  
8 future, when there's more than one year exposure,  
9 to really probably focus more on the newer one if  
10 it's somehow better. Thank you.

11 DR. NELSON: Dr. Page Crew will comment  
12 on the two different formulations.

13 DR. CREW: So that's an excellent  
14 question. And in our review of the FAERS  
15 analysis, we did record which version of  
16 deferasirox, which brand patients were using. And  
17 among the 162 cases, 151 patients were using  
18 Exjade brand. And then, two patients were using  
19 Jadenu brand, and two patients were using Asunra  
20 brand. And there were seven patients that, based  
21 on the time at which the report was made and the  
22 time at which they were taking deferasirox, we



1 felt that it was probable that they were using the  
2 Exjade brand based on approval dates.

3 DR. ROBIE SUH: One comment. The -- just  
4 additional information. The Jadenu was a recently  
5 approved film coated tablet version of  
6 deferasirox. Whereas the Exjade, you know, was a  
7 dispersible tablet formulation.

8 DR. CREW: This is Page Crew. I'll make  
9 one additional comment about the dosing  
10 differences. So, for example, the starting dose  
11 of Exjade brand is 20 milligrams per kilogram,  
12 versus the starting dose of the Jadenu brand is 14  
13 milligrams per kilogram.

14 DR. ROBIE SUH: It's Kathy Robie Suh that  
15 made that earlier comment.

16 DR. HUDAK: Dr. White.

17 DR. WHITE: Michael White. Going  
18 through the literature review and the data you  
19 guys provided us, it seems as if the lower liver  
20 burden, oh pardon me, the lower iron burden  
21 subjects had more adverse events. And just --  
22 there's a summary under five in the literature

1 overview, serum creatinine increase at any given  
2 dose of deferasirox. I'll use Exjade just because  
3 it's easier to say. Serum creatinine increases  
4 occurred more frequently in patient's receiving  
5 infrequent blood transfusions. And those with  
6 lower liver iron concentration and serum ferritin.  
7 And renal tubular damage, a similar observation.  
8 Lower -- lower iron burden, had more side effects.  
9 Or more damage. And transaminase elevation, liver  
10 iron content less than 7 milligrams of iron per  
11 gram dry weight, had 5.6 percent frequency of  
12 transaminase elevation compared to one percent of  
13 the other subjects with a higher iron burden. Can  
14 you help me understand that? Or are we looking  
15 into why there might be this discrepancy where you  
16 have lower iron and higher complications?

17 DR. WALDRON: I will try. The  
18 deferasirox is a very potent chelator. And as  
19 such, it is able to remove iron from tissue. The  
20 -- the pre-clinical studies did show a similar  
21 finding in animal models, in which there was more  
22 animal adverse events in animals that were iron

1 loaded than were not iron loaded. And so  
2 simplistically, the chelator of the deferasirox  
3 will pull iron out of tissue. And it will pull  
4 excess iron out of tissue, until it gets to the  
5 point where it may be pulling no longer the excess  
6 iron. But it may be pulling essential iron. Iron  
7 that is a component of cytochromes and other iron  
8 containing proteins. So, the -- the iron appears  
9 to act, the transfused iron appears to act as a  
10 buffer. And to allow, and of course this is the  
11 purpose of it, to remove tissue iron. But  
12 because, well when iron chelator then can go too  
13 far. And, as always, we're looking for that just  
14 right. And so that's the impression that one gets  
15 from reading the non-clinical literature and  
16 reading the clinical literature about that  
17 association. Hopefully that's an answer. I'll  
18 try again if it's not.

19 DR. WHITE: It sort of answers the  
20 question. But it brings up the other question of  
21 should we be more circumspect in the way we're  
22 using the iron chelation therapy, if those with a

1 lower iron burden are at higher risk for problems.

2 DR. WALDRON: Well, to some extent, that  
3 is reflected in the label where, for example, the  
4 patients who have non- transfusion dependent  
5 thalassemia, which is restricted to patients age  
6 10 and over, have a -- the maximum dose for that  
7 population, is 20 milligrams per kilogram per day.  
8 Whereas, for the transfusion dependent population,  
9 it's up to 40 milligrams per kilogram per day. So  
10 in that -- to that extent, it is reflected in the  
11 label. Another component of the current label is  
12 the recommendation to stop use when the serum  
13 ferritin level is less than 500 micrograms per  
14 liter. But, the other component of that is, well,  
15 is 500 right? Is there something different?  
16 Should there be some other dose alteration prior  
17 to that? Those are aspects of our ongoing review  
18 of this concern. Thank you. Oh. And Kathy --  
19 Dr. Kathy Robie Suh wants to make a comment.

20 DR. ROBIE SUH: Just also to add. Kathy  
21 Robie Suh here. That, of course, the use of  
22 Exjade, the use of these chelators in these

1 patients is -- I've had some benefit risk just as  
2 all of our products do. I'm concerned with  
3 build-up of iron, particularly in cardiac tissue,  
4 which would cause the demise. The first approval  
5 of Exjade was for patients with transfusion  
6 dependent. That was in -- and because of the  
7 known ongoing need. And a body does not have a  
8 way to get rid of iron normally. Normally the  
9 body conserves iron very much. And that tissue  
10 toxicity, particularly the cardiac effects leads  
11 to -- it leads to a lot of the morbidity and  
12 mortality in this particular patient population of  
13 -- in non-transfusion dependent thalassemia  
14 patients, you'd know you have the same physiologic  
15 process going on. And do you want to wait until  
16 iron load has gotten to a certain, you know,  
17 possibly damaging levels before starting chelation  
18 therapy. And that's generally not advisable in  
19 the -- in the practice of medical. But certainly,  
20 we know that Exjade has toxicities. So -- so as  
21 Peter has said, it's reflected in the label that  
22 we have now. I think it was most recently updated

1 in August of 2016 with additional heightening of  
2 -- heightenings of the warnings with regard to  
3 renal and hepatic toxicities. So, you know, and  
4 we continue to -- to look at how to best reflect  
5 and convey that information.

6 DR. HUDAK: I think we have three  
7 questions. We'll do Dr. Jones and then Dr.  
8 Callahan and then back to Dr. White.

9 DR. JONES: Brigitte Jones. I was just  
10 wondering in your review, were you able to look at  
11 the level of fever related to risk of toxicity?  
12 Since, in the report, it just says fever. And I  
13 didn't see any specifics in any of the cases of  
14 how high the temperature is. And since fever is  
15 on a spectrum, I'm wondering if children with  
16 higher temperatures may be at increased risk for  
17 dehydration. And therefore, may be at increased  
18 risk for toxicity?

19 DR. WALDRON: Because we had the two  
20 data sets, we'll ask the safety evaluators to  
21 comment on FAERS. And then Dr. Gelperin to  
22 comment on the clinical trials.

1 DR. PATANAVICH: Okay. This is Saharat  
2 Patanavich. Safety Evaluator. DPV. And  
3 unfortunately, with the limitation of the  
4 spontaneous poison FAERS, we have limited  
5 information with regards to the degree of the --  
6 the fever. So, unfortunately, we did not capture  
7 that information in the FAERS.

8 DR. GELPERIN: In the clinical trial  
9 data, we were looking at coded clinical adverse  
10 events, which don't include actual measurements of  
11 the amount of fever. So, it just would be like a  
12 MedDRA code for fever. Or pyrexia. So we -- we  
13 would not have that information. We could --  
14 well, I'll stop there.

15 DR. JONES: So in the five-year, the  
16 study that you're reviewing now, is there discrete  
17 temperature data that could be looked at?

18 DR. GELPERIN: The five-year pediatric  
19 registry had a -- an abbreviated safety data  
20 collection. So, for instance, non-serious  
21 clinical adverse events would not necessarily have  
22 been ascertained. So there's no reason to think

1 we would capture all of the occurrences with  
2 fever. I guess I'll also say, that for our  
3 current analysis, we're not so much focused on  
4 fever as being of interest, as trying to identify  
5 predictors so that we could avoid the sort of  
6 thing that happened in the in index case. We're  
7 trying to understand what would be the early  
8 warning signs. How could you identify a child  
9 where the drug should really be stopped? Or the  
10 dose should be reduced. And, so the question that  
11 the Advisory Committee posed to us, would fever be  
12 one of those things? And then, we added to that  
13 question, well, how about dehydration? Like  
14 diarrhea. And -- and so that's where our thinking  
15 is. We're not so much focused on fever as being  
16 of interest in itself, as we're really trying to  
17 come up with predictors to avoid severe toxicity.  
18 Especially in young children.

19 DR. JONES: Yes. I was just thinking  
20 that fever might be an early predictor in a child  
21 that had a really high fever, they may become  
22 dehydrated more quickly. Or have more severe



1       dehydration that could lead to toxicity. So that  
2       might be an early indicator that would be easy for  
3       parents to identify.

4                 DR. GELPERIN: Yeah. I mean, I think  
5       philosophically, we're on the same page that  
6       you're on. And we're -- we're thinking of  
7       actually a sort of -- acute childhood illnesses  
8       are, especially in little three year old children.  
9       You know, they kind of --. You know, you do worry  
10      that these little guys can get dehydrated pretty  
11      quickly. So, yeah, we're on the same page that  
12      you're on.

13                DR. CALLAHAN: David Callahan. I'm  
14      looking at Table 4, when you're talking about  
15      dehydration adverse events, with evidence of  
16      kidney injury. In the slide after that, on the  
17      analysis, in the last sentence, it talks about a  
18      similar injury pattern, where it's not observed in  
19      the small number of dehydration events, where DFS  
20      therapy was interrupted or adjusted. So my  
21      concern is, there's really no statistical  
22      significance. And so I -- I wonder why that is

1 even in there. It's almost misleading.

2 DR. GELPERIN: Well this -- maybe we  
3 could go to the backup slides and I can show you a  
4 listing of those specific individuals from the  
5 study. Right. This was a post-talk analysis of  
6 clinical trial safety data. And it would not  
7 support inferential testing. So what we were  
8 really trying to do was to identify what really  
9 happened. And so we had -- we were able to  
10 identify a data set, where we had a lot of  
11 laboratory results. And we have information about  
12 individual study subjects. And, so I can show you  
13 a little bit more about our thinking. We have the  
14 backup slide number -- it's actually the last  
15 backup slide. I'm afraid it's probably hard to  
16 see. But, the thing that I found striking is  
17 that, these are eight unique study subjects who  
18 experienced a dehydration adverse event in Study  
19 107. That's 10 percent of the subjects who --.  
20 So, that's about 10 percent of the overall number  
21 of subjects who experienced a dehydration adverse  
22 event. These are study subjects who had a normal

1 serum creatinine prior to the diarrhea occurring.  
2 And what you can see in this line listing, is that  
3 after diarrhea, when their deferasirox dose was  
4 continued, they went on to develop a laboratory  
5 evidence of kidney injury that is now in the range  
6 where the labeling calls for withholding therapy.  
7 So, the logic that we're trying to put forward  
8 here is that since 10 percent of the study  
9 subjects went on to develop a level of kidney  
10 injury, that would call for withholding therapy,  
11 that you might think that it would make sense  
12 during an acute pediatric illness with  
13 dehydration, such as diarrhea, that it would -- it  
14 would be prudent to withhold the dose. Since  
15 there's no acute benefit. So -- so that's the  
16 thinking. It's not inferential testing.

17 DR. CALLAHAN: But am I correct in  
18 saying that you don't have any data to show that  
19 withholding the dose prevents kidney injury?

20 DR. GELPERIN: That's correct. From the  
21 data set that we have available, we -- we don't  
22 have, we can't show that. No. But I, you know, I

1 think as Dr. Waldron has pointed out, the  
2 half-life of this drug is such that even  
3 withholding the therapy, would not necessarily  
4 assure that you don't continue to have a drug  
5 effect. Especially if you do have some acute  
6 kidney injury going on. I guess the other thing I  
7 would just show you, is it's, or maybe you know,  
8 it's not in doubt that this drug is nephrotoxic.  
9 It's labeled. This pivotal trial, the comparator,  
10 was deferoxamine. There was an imbalance for  
11 laboratory parameters of confirmed abnormalities  
12 for both liver injury and kidney injury. So it's  
13 not in question whether the drug can cause a toxic  
14 effect. The question is, how do we identify an  
15 early predictor to avoid serious injury,  
16 especially in young children?

17 DR. WALDRON: And I'll just add one more  
18 comment. In the realm of safety data, the  
19 expectation that we would have a statistically  
20 significant difference, is non-existent, because  
21 the trials are not powered for that purpose. And  
22 the - - there was not a randomization to what

1       happened. And so, we - - we do look at just this  
2       descriptive picture of what do we see in this  
3       context Part I? And then Part II is that the  
4       concern as expressed by the nephrology review in  
5       the Division of Pediatric Maternal Health review,  
6       that the context of these acute illnesses with  
7       dehydration and/or fever, may put a child in a  
8       situation in which, just with the child in front  
9       of you, no laboratory information. The concern  
10      that their renal status has moved from their  
11      baseline into that elevated creatinine context.  
12      Which, we think is a context in which continuing  
13      the drug would be more risky than withholding it  
14      for that temperature. Hopefully that answers your  
15      questions.

16                   DR. HUDAK: Dr. White.

17                   DR. WHITE: I think you guys have been  
18      sort of answering my questions. You've been  
19      going. Thank you for this effort. It was brought  
20      about by a patient, a family that came to one of  
21      our meetings, and our patient advocate at the  
22      time, who were concerned about using these drugs

1 and how to predict before they went to the doctor  
2 and found out that their creatinine was elevated.  
3 What could they do to hopefully prevent that  
4 without going to the doctor? And I think you guys  
5 are heading in the right direction. I appreciate  
6 it.

7 DR. HUDAK: Dr. Cnaan.

8 DR. CNAAN: Two more suggestions. You  
9 note, in first in response to Dr. Jones, you noted  
10 that you get the fever information from the MedDRA  
11 coding of events. I wonder if the trial just  
12 records plain old vital signs. And therefore, you  
13 might get it from there rather than from events.  
14 And the other thing that I was curious about is  
15 this does not include sickle cell patients, which  
16 is fine. It includes a collection of several  
17 diagnoses. I wonder if you looked at whether  
18 diagnosis matters.

19 DR. GELPERIN: Yes.

20 DR. WALDRON: Or course that's a -- a  
21 good question. We do have that data. We have the  
22 indication for the use of the drug. We did not --

1       because one, the overall majority of patients do  
2       have transfusion dependent thalassemia. The  
3       remainder of the patients, excluding the sickle  
4       cell patients, which are the next most common  
5       group. Or the next most common indication for  
6       transfusion dependency. The other numbers are  
7       very small. And so, we have not been able to use  
8       those as independent indicators of predictive --  
9       prediction of adverse events. I'll ask Dr.  
10      Gelperin if she has any additional comments.

11                 DR. GELPERIN: Well, for the five-year  
12      pediatric registry, actually we have been  
13      evaluating for the coded clinical adverse events,  
14      which is different from the laboratory  
15      abnormalities. But for the coded clinical adverse  
16      events, we have looked at them by underlying  
17      disease condition. And, we haven't found any --  
18      any striking differences thus far. But that's  
19      still in review.

20                 DR. HUDAK: Dr. Zuppa and then Dr.  
21      Sayej.

22                 DR. ZUPPA: I think it's a -- a really

1 good point that was brought up. Fever is really  
2 in some ways a surrogate for something else that's  
3 going on. But it's really non- descript. So, if  
4 you take a child with an otitis media and a fever,  
5 that child will look really different than a child  
6 with influenza and a fever, will look really  
7 different than a child who's having, you know,  
8 rotavirus or norovirus and vomiting and diarrhea.  
9 So, I don't know if, I mean, I feel like we're  
10 making some big decisions based on fever, which is  
11 pretty non- descript. And can represent so many  
12 different clinical scenarios.

13 DR. SAYEJ: She beat me to the question.  
14 My -- my question was in a similar perspective.  
15 In order to determine predictors of disease or  
16 predictors to the development of dehydration or  
17 nephrotoxicity or hepatic toxicity, we need to  
18 figure out what other variables are contributing  
19 to this. Such as the indication for use of  
20 Exjade. But also, at the same time, the illness  
21 that's going on with the patient. The cause of  
22 the fever. Is it otitis media versus pneumonia



1 versus an acute gastroenteritis? From a hepatic  
2 impairment perspective, it's not unusual to see a  
3 slight bump in the liver enzymes. Even up to  
4 twice upper normal limit. Or three -- three times  
5 upper normal limit. And that depends on the  
6 disease processes undergoing that's causing the  
7 hepatic impairment. Other confounders that could  
8 potentially be looked at, include what other  
9 medications were these patients on. What is their  
10 splenic function? Are they asplenic or do they  
11 have splenic suppression going on? Do they  
12 have portal hypertension from a progressive  
13 disease from the -- the chelation therapy? Or, do  
14 they have a progressive liver disease to begin  
15 with because of that? So.

16 DR. WALDRON: Submit the analysis of the  
17 results with the transaminase elevation. There  
18 are two analyses. But one that Dr. Gelperin  
19 presented was patients who had baseline normal ALT  
20 AST. And so, be -- I think, and I'll ask you.  
21 But, I would consider that to be unlikely to have  
22 cirrhosis or portal hypertension in that context.

1 DR. HUDAK: Dr. Turer.

2 DR. TURER: So, this may have a slip or  
3 it may have insightful, which was the use of  
4 diarrhea and dehydration. I was just looking at  
5 how this drug is excreted. And it's primarily 84  
6 percent through feces. So the question is, what  
7 if diarrhea has some impact on metabolism of the  
8 drug. So, you know, determining in cases where  
9 there's diarrhea versus just fever, could that be  
10 one of the predictors? Could, you know, rapid  
11 diarrhea alter excretion of the drug?

12 DR. WALDRON: That's a hypothesis. That  
13 we would have to be able to measure drug levels.  
14 And (inaudible), I think to answer that question,  
15 and then, of course, I have to capture that, you  
16 know, capture children with diarrhea. We wouldn't  
17 -- it's a very difficult question to answer, I  
18 think it's my answer, so. An interesting  
19 hypothesis though.

20 DR. HUDAK: Other comments or questions?  
21 So I have - - I have just a procedural question.  
22 So the review by Pediatric Nephrology within the

1 FDA recommended that the medication be temporarily  
2 discontinued in the presence of clinical and/or  
3 laboratory evidence or dehydration. But the  
4 safety review is continuing. So how does that  
5 play within the sphere?

6 DR. ROBIE SUH: Kathy Robie Suh.  
7 Certainly internally we -- we have been working  
8 with OSE. We've been looking at all of, you know,  
9 input from all of our relevant divisions. And,  
10 you know, the Maternal and Pediatric Safety Team  
11 that we have here. And our experts, nephrology,  
12 you know, the question of how to -- how to convey  
13 information that is at least partly in the  
14 practice of medicine. Certainly so many things --  
15 so many things can cause temporary and rapidly  
16 changing things among -- within a sick patient.  
17 And so we're going to continue to work together.  
18 We will draw the whole -- the whole group together  
19 and factor in all of our input, including the  
20 input that we've received from the group today.  
21 And try to devise the best path for what to serve  
22 these patients.

1 DR. HUDAK: I just have two other  
2 questions if I can. I may have missed this first  
3 one. And someone may have referenced this. But,  
4 it was in effect to the patient's that had  
5 documented renal or hepatic injury. Were these  
6 things reversed over time? Or was there an  
7 incremental injury that was sustained?

8 DR. WALDRON: The FAERS data, some of  
9 the cases would have reported a -- a resolution.  
10 And some of them wouldn't. But in general, and  
11 then I'll ask Kate to comment. Did you want to  
12 comment? Okay. In general, all these, I go to  
13 resolution with a rare exception of those  
14 catastrophic cases that don't. But I'll ask Kate  
15 to comment on the clinical trial data.

16 DR. GELPERIN: In the clinical trial  
17 data, well, in Study 107, for instance, the line  
18 listing that I showed you. None of -- none of  
19 those nuance had acute injury cases progressed to  
20 acute renal failure. Or required -- none of them  
21 required dialysis. And, in general, the -- the  
22 acute kidney injury that I see in the clinical

1 trials, generally does resolve with  
2 discontinuation of the drug. So there does seem  
3 to be a lot of value in identifying what is that  
4 moment when the drug should be stopped?

5 DR. WALDRON: The one renal injury that  
6 is frequently but not always reversible, is the  
7 tubulopathy or the Fanconi Syndrome like picture.  
8 That is reversible in many cases. But in others,  
9 there's a persistent need for electrolyte  
10 replacement.

11 DR. GELPERIN: Oh yeah. I'm sorry.  
12 That's right. For the Fanconi Syndrome, it -- the  
13 resolution is a much, in the clinical trial data,  
14 it takes longer after the drug is stopped.

15 DR. HUDAK: I had noticed on your --  
16 your backup slide, that the interval between the  
17 onset of the AE and the laboratory draw was up to  
18 22 days, I think, in patients. And they still had  
19 elevated creatinines above baseline. So, I'm  
20 presuming that you have information that further  
21 down the pike, that these values sort of came back  
22 toward the pre AE numbers?

1 DR. GELPERIN: For those eight subjects  
2 with the nuance had acute kidney injury after  
3 diarrhea, where the drug had been continued. We  
4 actually worked with Novartis to -- to look into  
5 the time course for each of those. And, right,  
6 they all eventually resolved. Some more quickly  
7 than others. Yeah.

8 DR. HUDAK: And then, I guess, my last  
9 question is, I'm a little bit, I don't know the  
10 actual clinical trial structure for this drug. In  
11 one case, you referred to it as an open label.  
12 And in the other case, you refer to it as a double  
13 blind with clinical long term extension. So the  
14 question is, do you have any information in these  
15 patients, who might have been at one time on a  
16 placebo medication? Whether --.

17 DR. GELPERIN: I'm sorry. That -- if  
18 there -- if it says double blind, that's a typo.

19 DR. HUDAK: Okay. All right. Well the  
20 question stands. Is there any data base that  
21 would look at patients with these particular  
22 diseases who are, at one time, treated with the

1 placebo? And again, look for AEs such as fever  
2 and dehydration.

3 DR. GELPERIN: The comparator in Study  
4 107 is deferoxamine. And so I can show you --  
5 well, so your -- the answer to the data I've had  
6 access to is no. But let -- maybe Dr. Robie Suh  
7 can talk about that.

8 DR. ROBIE SUH: Deferoxamine, we just --  
9 the control that's used in the original studies.  
10 You know, it's administered by a subcutaneous  
11 infusion. Which is really an odious kind of  
12 treatment. And has -- its continuous infusion for  
13 most of the days of a week. And, for obvious  
14 reasons, there was not a control -- blinded  
15 controlled situation in that trial. But -- but  
16 also, for obvious reasons, compliance with  
17 Desferal was in the issue also. And so we have, I  
18 think, some historical, you know, historical  
19 information on what happens when patients do not  
20 comply. And that -- that informs the  
21 understanding of the outcomes for these patients  
22 who don't receive any chelation therapy.

1 DR. KASKEL: Rick Kaskel. Nephrology.  
2 I heard the comment of the Fanconi Syndrome, and  
3 the tubulopathy. I didn't see the numbers in the  
4 tables as to how many those patients are in the  
5 follow-up registry. That's a significant long  
6 term affect. So we have a couple of things. As a  
7 nephrologist, I'm going to comment on this. And  
8 I've done work in nephrotoxicity. There's two  
9 types. You've got a (inaudible) acute injury with  
10 a drop in function evidenced by (inaudible) the  
11 creatinine. You have a tubulopathy apparently.  
12 Which may persist after the creatinine comes back  
13 to normal. A recent report of long term follow-up  
14 of acute kidney injury in the neonate and early  
15 infancy, shows that even though there's a  
16 resolution of serum creatinines, there's a long  
17 term risk for development of chronic kidney  
18 disease as that patient goes across the lifespan.  
19 So --.

20 DR. WALDRON: Right. The neonates, what  
21 group were they -- did they have a Fanconi  
22 Syndrome?



1 DR. KASKEL: No. Those were AKI from  
2 various causes.

3 DR. WALDRON: Oh I see. Generic AKI.

4 DR. KASKEL: Right

5 DR. WALDRON: Okay good. Thank you.

6 DR. KASKEL: But early infants were  
7 included in that study. So obviously, long term  
8 follow-up from this cohort is needed. That's one.  
9 Two, a tubulopathy that persists, that wasn't  
10 there prior to the exposure, that's very  
11 significant. That should resolve. You shouldn't  
12 be left with a permanent Fanconi Syndrome or  
13 aminoaciduria, unless it was a very serious hit.  
14 So I think you need some more information on that.  
15 And moving forward, if I were to look at a  
16 prospective study, some of these issues, you're  
17 talking about, can be addressed with some simple  
18 measurements of vital signs and weight. We talk  
19 about dehydration. We're throwing that around.  
20 Dehydration, constipation and a fever. Or some  
21 diarrhea. Well, how about some change in baseline  
22 body weight, prior to giving the drug. Even at

1 home, using a home scale. So to see if there's a  
2 five percent reduction or ten percent reduction in  
3 body weight, placing that infant at risk. And  
4 two, if we were going to move forward with some  
5 biomarker work, we have very good studies today to  
6 show that you can, in an emergency room, using  
7 some of the -- the newer methods to assess acute  
8 kidney injury, such as NGAL, you can make a  
9 clinical assessment as to a patient at risk for  
10 acute kidney injury. That's a prospective study.

11 DR. HUDAK: Thank you Dr. Kaskel. I  
12 think we have one question from Dr. Havens on the  
13 phone.

14 DR. HAVENS: Yes thank you. Can you  
15 hear me?

16 DR. HUDAK: Yes.

17 DR. HAVENS: So the question was, were  
18 these results considered in the context of the  
19 serum ferritin? Now the point was made earlier  
20 that the people with lower serum ferritin actually  
21 had greater toxicity, perhaps from iron chelation  
22 at the level of the mitochondria. So if these

1 toxicities are actually greater in the dehydrated  
2 person. Or something with an already low  
3 ferritin, has that been considered as part of the  
4 issue? Thank you.

5 DR. WALDRON: Sure. Excuse me. Peter  
6 Waldron. The FAERS data generally do not report  
7 serum ferritins for the fever and dehydration  
8 cases. The clinical trial data, I also don't know  
9 whether I --. Okay, Dr. Kaskel, will comment on  
10 that. But it -- it is obviously something that  
11 we're wondering about too.

12 DR. KISHNANI: Hi. This -- this is  
13 Priya Kishani. I also had a question. This was a  
14 great conversation.

15 DR. WALDRON: Sorry we were -- I'm  
16 sorry. We were still answering the previous  
17 question. So if you would just hold your  
18 questions.

19 DR. KISHNANI: Oh I'm sorry. Yes. Yes.

20 DR. GELPERIN: Yeah. Just to say that  
21 serum ferritin is very important. We do have  
22 serum ferritin in the five-year registry data that

1 we're evaluating. But I think also, it might be  
2 worth talking about the published --. So the case  
3 series that Dr. Waldron's evaluating, serum  
4 ferritin has turned out to be extremely important.  
5 Again, a small number of cases. But -- but I  
6 think that that is going to be the emerging story,  
7 is how important the iron burden is, in terms of  
8 the toxicity of this chelator. Do you want to  
9 comment on those cases? No. Okay. Yeah.

10 DR. WALDRON: The liver failure, renal  
11 failure, hyperammonemia cases, there is a concern  
12 in that group that we were seeing some mismatch  
13 between the dose and the iron burden. And, but  
14 this is an ongoing review, and so this is just a  
15 concern. I can't go any further than that.

16 DR. HUDAK: Okay. Dr. Kishnani, you can  
17 ask your question now.

18 DR. KUSHNANI: Yes. Sorry, I -- I agree  
19 with a lot of the comments. I just had one  
20 overall question. It's hard to really piece out  
21 these characteristics of the patient. But  
22 overall, was it possible to look at, was it a

1 younger age that was more vulnerable? A lower  
2 weight of these patients? A longer duration on  
3 treatment? Were there any such features that  
4 could, you know, help us in a direction of far  
5 more caution? You know, simple but able to be  
6 done rather quickly.

7 DR. CREW: Page Crew answering this  
8 question. We did collect demographic  
9 characteristics of the FAERS cases that we  
10 reviewed. So I can share with you, for example,  
11 the median age of the cases that we included was  
12 eight years. The range was 2 to 15.9, which were  
13 the limits of age that we set for analysis. The  
14 median age was 8.2. And in terms of patient  
15 weight, we did not always have a value for that.  
16 And when we did, it was unclear whether it was  
17 pounds or kilograms. Which made the assessment  
18 complicated. So unfortunately, we aren't able to  
19 answer those important questions with this FAERS  
20 data.

21 DR. KISHNANI: I see.

22 DR. HUDAK: I don't see any further

1 questions. So, next steps on this. Dr. Nelson.

2 DR. NELSON: Well, as you can see, this  
3 has been a lot of work. And involving a number of  
4 people. And also going back and forth with the  
5 sponsor around new data sets. And, as questions  
6 emerge, looking at those questions over time, I  
7 don't think anyone wants to drag this out too  
8 long, and would like to wrap this up as soon as  
9 possible. So I think there's a hope that whether  
10 -- whether there'd be a conclusion and some  
11 recommendations that you could see at the  
12 September meeting or not, I think is an open  
13 question. But that's a goal. But whether it will  
14 take a little more time, I guess depends upon how  
15 the analysis proceeds. So, you know, there's been  
16 a lot of interesting comments. And I've noted  
17 people taking notes about how to look at those  
18 data. And that will be taken into consideration.  
19 But our hope is that, we could wrap this up with  
20 another presentation in the near future. Which  
21 would include, perhaps, recommendations that you  
22 could then react to more concretely at that time.

1       So I don't know if anyone wants to add anything to  
2       that summary.

3                   DR. JONES:  The one thing I would add,  
4       hi this is Chris Jones, Director of Division of  
5       Pharmacovigilance II.  So as you could tell from  
6       the presentations today, there are a lot of  
7       different disciplines involved.  And in the  
8       agency, we will open a track safety issue for  
9       things that we think are important that we really  
10      want to dig into and look at further.  And this is  
11      one of those issues.  So there -- as Skip  
12      mentioned, there are many disciplines that are  
13      involved here.  The team after this meeting today,  
14      listening to some of this feedback, we're going to  
15      go back.  Focus.  There's an additional analysis  
16      that we're expecting from the sponsor.  We'll be  
17      looking at that.  And we're hopeful we can wrap up  
18      the track safety issue in the coming months.  At  
19      this point, whether we'll come back to the PAC  
20      and present, that's more of an open issue.  What  
21      we're really focused on the team at this point, is  
22      to try to identify some predictors.  And can we

1 put together some text in the labeling that will  
2 help a physician make a decision about whether he  
3 should interrupt or disrupt the dosing of this  
4 drug.

5 DR. HUDAK: Okay. I think that wrapped  
6 up the discussion. I'd like to express the  
7 Committee's thanks to the individuals who brought  
8 this issue to our attention back in September of  
9 2015. And -- and thank the FDA very much for a  
10 very comprehensive look see into this matter with  
11 their FAERS and the sponsors databases. I think  
12 it's been very illuminating to all. So I guess  
13 with that, I think we're scheduled for a break.  
14 We're a little bit early I think. I don't know,  
15 do we have people arriving at a particular time?  
16 Is it 10:45 or are they here? Or how should we  
17 proceed?

18 DR. NELSON: Well we can check and see.  
19 We could either do Kuvan before the break or after  
20 the break. Depending on whether the people for  
21 Kuvan are present and accounted for. So.

22 DR. Spauldingthe DPMH presenter is here. The



1 DPMH presenter is here for Kuvan.

2 DR. HUDAK: Okay. Is that the only  
3 presenter? We have everybody for that product  
4 here?

5 DR. NELSON: Pam, are we ready to go?

6 MS. WEINEL: Yeah.

7 DR. NELSON: The answer is yes.

8 DR. HUDAK: Okay. Well we will proceed  
9 with Kuvan. Excellent.

10 DR. HUDAK: Okay. Dr. Spaulding, are  
11 you ready?

12 DR. SPAULDING: Yes.

13 DR. HUDAK: Could you say the pertinent  
14 information about yourself --

15 DR. SPAULDING: Sure.

16 DR. HUDAK: -- to the group?

17 DR. SPAULDING: Thank you.

18 DR. HUDAK: Thank you.

19 DR. SPAULDING: My name is Jacqueline  
20 Spaulding and I am a medical officer in the  
21 Division of Pediatrics and Maternal Health. I'll  
22 be presenting the pediatric focus for safety

1 review for Kuvan. This slide shows the outline of  
2 today's presentation. Kuvan is a phenylalanine  
3 hydroxylase activated drug product containing  
4 Sapropterin. It is a synthetic preparation of the  
5 dihydrochloride salt of naturally occurring  
6 Tetrahydrobiopterin or BH4 and is indicated to  
7 reduce blood phenylalanine levels in patients with  
8 Hyperphenylalanemia or HPA due to BH4 responsive  
9 phenylketonuria or PKU. The recommended starting  
10 dose of Kuvan for pediatric patients with PKU ages  
11 1 month to 6 years is 10 milligrams per kg once  
12 daily. And the recommended starting dose of Kuvan  
13 for patients ages 7 years and older is 10 to 20  
14 milligrams per kg once daily. The dose should be  
15 adjusted within the range of 5 to 20 milligrams  
16 per kg once daily, based on the control of blood  
17 phenylalanine levels. Kuvan tablet was originally  
18 approved in 2007 for reduction of Phenylalanine  
19 levels in patients 4 years of age and older and  
20 there the approval of Kuvan powder for oral  
21 solution in 2013 for the same indication. Of  
22 note, this safety review was prompted by the

1       expanded pediatric indication to include pediatric  
2       patients 1 month to 4 years of age in 2014. In  
3       the next few slides I will highlight relevant  
4       safety information currently included in Kuvan  
5       labeling. In Section 5 Warnings and Precautions,  
6       included is hypersensitive reactions,  
7       hypophenylalanemia, monitoring blood phenylalanine  
8       levels during treatment and treat all patients  
9       with a phenylalanine restricted diet. Continuing  
10      on, monitoring patients with hepatic impairment,  
11      monitor for hypertension when co-administering  
12      Kuvan and drugs known to affect nitric  
13      oxide-Mediated vasorelaxation, monitor when  
14      co-administering Kuvan and Levodopa and monitoring  
15      for hyperactivity. The sponsor included data from  
16      two studies and their pediatric efficacy  
17      supplement, which was approved in 2014. One study  
18      supported the short-term efficacy of Sapropterin  
19      and BH4 responsive patients 0 to 6 years of age.  
20      It was a four week open label PK study in 94  
21      patients 6 years of age and younger. Patients  
22      received Kuvan 20 milligrams per kg per day as a

1 single daily dose for four weeks. The other study  
2 was a six-month open label one arm trial to  
3 evaluate safety, efficacy and baseline neuro  
4 cognitive function in 57 patients with PKU ages 0  
5 to 6 years. The efficacy data for this study  
6 indicated that there was a reduction in blood  
7 phenylalanine levels following treatment with  
8 Kuvan for four weeks in pediatric patients ages 0  
9 to 6 years who were maintained on a stable  
10 phenylalanine diet. There was insufficient data  
11 to support long-term efficacy because the trial  
12 did not control of dietary phenylalanine intake  
13 for the remainder of the six-month treatment  
14 period. In the PK study because there were safety  
15 concerns about a higher incident of  
16 hypophenylalanemia in patients dosed with  
17 milligrams per kg, especially in the  
18 younger age groups. This led to the decision to  
19 recommend the 10 milligram per kg starting dose  
20 for children less than 7 years of age and a  
21 starting dose range of 10 to 20 milligrams per kg  
22 for patients older than 7 years of age. The

1 observed safety profile of Kuvan in the six-month  
2 efficacy safety trial data with post-marketing  
3 data provided the applicant was consistent with  
4 their labeling for Kuvan. Following Kuvan's  
5 pediatric approval to reduce phenylalanine levels  
6 in pediatric patients 1 month to 4 years of age  
7 with HPA due to BH4 PKU in conjunction with a  
8 phenylalanine restricted diet, the pediatric use  
9 sub-section of Kuvan labeling was updated to  
10 cross-reference to the relevant sections in  
11 product labeling where information from both  
12 pediatric studies was added. Efficacy and safety  
13 of Kuvan has not been established in neonates. In  
14 pediatric patients ages 1 month to 16 years, the  
15 efficacy of Kuvan has been demonstrated in trials  
16 of less than six weeks duration. The  
17 effectiveness of Kuvan alone on reduction of blood  
18 phenylalanine levels beyond four weeks could not  
19 be determined due to concurrent changes in dietary  
20 phenylalanine intake during a multicenter open  
21 label single arm study in 57 patients ages 1 month  
22 to 6 years who were defined as Kuvan responders

1 after four weeks of Kuvan treatment and  
2 phenylalanine dietary restrictions were treated  
3 for six months of Kuvan of 20 milligrams per kg  
4 per day. The safety of Kuvan has been established  
5 in children younger than 4 years in trials of  
6 six-month duration and in children 4 years and  
7 older in trials of up to three years in length.  
8 Next, we will examine the pediatric-focused adverse  
9 events for Kuvan. We identified pediatric reports  
10 with a serious outcome for Kuvan from January 1st,  
11 2013 to July 31st, 2016. On the left side of the  
12 slide we see that 53 cases were reviewed and  
13 excluded. The chief reasons for exclusion were a  
14 transplacental exposure and other reasons. Under  
15 other reasons, cases were excluded to the  
16 following in decreasing order, adult patients that  
17 were coded with the wrong age, including two  
18 deaths, duplicates, indication related,  
19 counterfeit drugs and overdose. The right side of  
20 the slide shows the remaining 47 reports in the  
21 pediatric case series with a serious outcome, this  
22 included a total of four cases reported as an

1 outcome of death. There were four reported death  
2 cases. The age range for these patients was 10  
3 months to 7 years. Two fatal cases contained  
4 insufficient clinical information. In the third  
5 death case a  
6 year-old male with a history of atypical  
7 PKU and seizures died in the middle of the night  
8 after having a seizure. He had profound motor and  
9 cognitive disease and had been on Kuvan for three  
10 years at the time of his death. The seizure and  
11 death were contributed to his underlying medical  
12 condition. The remaining death case involved a 15  
13 month-old female with a history of atypical PKU  
14 who had been receiving Kuvan 600 milligrams orally  
15 once daily for approximately 1 month when she  
16 experienced apneic events after receiving a dose  
17 of Kuvan. Concomitant meds included baclofen,  
18 gabapentin, bromide and Carbidopa/levodopa and  
19 glycopyrronium. The event was reported as severe  
20 and the patient died two days after the report  
21 apneic events. Of note the patient did have a DNR  
22 status. We reviewed 43 reports that described

1 serious non-fatal unlabeled events. Of the 43  
2 reports, 26 had alternative plausible explanations  
3 for the events, such as PKU, history of seizures  
4 or infection. Twelve cases lacked clinical  
5 information for proper assessment and two lacked a  
6 temporal relationship to Kuvan use. The remaining  
7 three cases we could not exclude the role of  
8 Kuvan. There were two cases of the unlabeled  
9 event of epistaxis identified. The first case  
10 involved a 2 year-old female with PKU and history  
11 of seizures but no prior history of nose bleeds.  
12 This patient developed daily epistaxis after  
13 starting Kuvan 100 milligrams orally daily for  
14 PKU. No concomitant meds were reported. Seizure  
15 frequency upon starting Kuvan was reported as  
16 daily. The second case involved a 9 year-old boy  
17 who experienced heavy nose bleed and some blood  
18 clots from his left nostril approximately 1 year  
19 after starting Kuvan 500 milligrams orally daily.  
20 This does is greater than 20 milligrams per kg for  
21 PKU. The events occurred weekly. No other  
22 clinical details were reported. There was one



1 case of the unlabeled event of insomnia  
2 identified. This case involved a 13 year-old boy  
3 who developed insomnia, agitation and psychomotor  
4 hyperactivity at an unknown time after starting an  
5 unknown dose of Kuvan for an unknown indication.  
6 The event was reported as resolved when on an  
7 unspecified date. In summary, no new pediatric  
8 safety signals have been identified for Kuvan.  
9 The plan is to monitor for Epistaxis and Insomnia  
10 in all patient populations. The Agency recommends  
11 continuing ongoing surveillance. And the question  
12 to the Committee is, do you agree? I'd like to  
13 thank all the individuals on the slide for their  
14 assistance in this presentation. Thank you.

15 DR. HUDAK: Okay. Thank you, Dr.  
16 Spaulding. It's now open for discussion. Dr.  
17 Anne.

18 DR. ANNE: This is Dr. Anne. You know  
19 in the warnings and precautions section of the  
20 product insert, you know, they discuss QTc,  
21 Correct QT Interval Prolongation in adults only,  
22 they only looked at 56 healthy adults. Is that

1 something that's worth evaluating -- it's more of  
2 a question. Is that something that's worth  
3 evaluating in the younger population that you're  
4 seeking approval for her, the 1 month to 16 year  
5 -- or more so, one to four year olds -- 1 month to  
6 year olds? The QTC decreased by about  
7 three milliseconds at the 20 milligram per kilo  
8 dose and then, the suprathapeutic dose it was  
9 negative eight milliseconds.

10 DR. HUDAK: Let me -- before we take  
11 that question, let me actually introduce the  
12 people who are here who will answer that question,  
13 introduce themselves.

14 DR. LEVIN: Hi, Bob Levin, Division of  
15 Pharmacovigilance.

16 DR. SWANK: Safety Evaluator, Division  
17 of Pharmacovigilance.

18 DR. GREENE: Patty Greene, drug  
19 utilization.

20 DR. SMPOKOU: Patroulos Smpokou,  
21 clinical reviewer, Division of Gastroenterology  
22 and Inborn Error Products.

1 DR. HAUSMAN: Ethan Hausman from  
2 Pediatric and Maternal Health. I want to see if I  
3 understand the question. So before we get into  
4 the topic of the question that FDA is proposing,  
5 your concern is something related to the QT  
6 prolongation, which is described in the adult  
7 population, but your question --

8 DR. ANNE: That's right. Okay. There's  
9 no evidence that was noted in the pediatric  
10 population.

11 DR. HAUSMAN: Okay. So my question to  
12 the GI folks, if you're familiar enough with the  
13 background and the development is, was there a  
14 thorough QT study done with the drug prior to even  
15 addressing an issue about going forward with the  
16 pediatric question?

17 DR. SMPOKOU: In terms of the adult  
18 indication I would have to go back and look and  
19 get back to you, so I don't have an answer at this  
20 point.

21 DR. HAUSMAN: Okay.

22 DR. LEVIN: Hi, Bob Levin. Did you -- I

1 think you mentioned there was a decrease?

2 DR. ANNE: There was a decrease in the  
3 Correct QT interval, yes.

4 DR. LEVIN: So one question, you're  
5 suggesting looking and doing a study in children,  
6 QT study. I guess one answer would be if there's  
7 a decrease there may not be a real indication to  
8 do such a study. The more there's an increase, of  
9 course, we might consider that.

10 DR. ANNE: I mean, you can have short QT  
11 syndrome, which can lead to ventricular  
12 arrhythmias and can -- and has been implicated in  
13 sudden death also. Again, albeit, it's not  
14 frequent.

15 DR. LEVIN: Right.

16 DR. ANNE: But it is -- this may be  
17 something to consider.

18 DR. LEVIN: Good point. We'll look into  
19 whether there's an actual dedicated QT study for  
20 that controls.

21 DR. HUDAK: Dr. Callahan.

22 DR. CALLAHAN: Just a follow-up. I

1 think in the 7 year-old boy they describe what was  
2 likely SUDEP up or Sudden Unexplained Death in  
3 Epileptic patients and some of those patients it  
4 may be a cardiac arrhythmia that triggers a  
5 seizure and a death. So I'd be interested if we  
6 had any EKG data on the patient prior to the child  
7 dying and even for the  
8 month-old female also -- again, any EKG  
9 baseline.

10 DR. SWANK: This Kim Swank from Division  
11 of Pharmacovigilance. Unfortunately, they did not  
12 provide any EKG data for either one of those  
13 cases.

14 DR. HUDAK: Dr. Kishnani, do you have a  
15 question?

16 DR. KISHNANI: Yes. I think one of them  
17 was already addressed. The reduced QTc was  
18 brought up because that was something I had to ask  
19 as well. My other question was about the patient  
20 that was on the 65 milligrams per kilogram dose,  
21 who was also, I believe, on levodopa and also was  
22 a DNR. Was there any understanding of such a high

1 dose and was any details around, you know, that  
2 event captured, such as EKG, et cetera?

3 DR. SWANK: This is Kim Swank. No --  
4 the only information that was provided in the  
5 review -- there was no EKG information, no other  
6 information surrounding the events, just that the  
7 patient developed apneic events shortly after  
8 receiving a dose the patient had been on for at  
9 least one month, but no other information, no.

10 DR. KISHNANI: I just had a follow-up  
11 question to that. So in the label I know we talk  
12 about lower dose like in a study of 10 milligrams  
13 per kilogram for the younger patients and then  
14 going up to 10 to 20 if there -- a limit, you  
15 know, for the upper level of the dose to say that  
16 this really something we have to be careful about.

17 DR. SMPOKOU: I think the answer to that  
18 question is no because, initially, there is a  
19 trial in terms of whether the patient is a  
20 responder and then there is -- of the dose  
21 upwards, based on blood phenylalanine levels. The  
22 recommended dose is up to 20, that is what was

1 studied in the clinical trials. In terms of  
2 whether usually people may go higher, I don't have  
3 that information, but conceivably based on  
4 response and based on total protein that the  
5 patient may be on, it could be that there might be  
6 a higher dose used in those patients.

7 DR. KISHNANI: So the question is, is  
8 this data worth capturing to know if there other  
9 events at a higher dose. I mean, it may not have  
10 resulted in death, but anything else? This is  
11 just a cautionary question because sometimes in  
12 pediatrics, you know, wavering from the labeled  
13 dose and is there any caution that's been put out  
14 about the certain dose, you know, this has not  
15 been studied or it's being investigated, et  
16 cetera?

17 DR. SWANK: This is Kim Swank. As far  
18 as the FAERS data, there were no other reports  
19 that indicated a patient was receiving higher than  
20 the recommended 20 milligrams per kilogram, but  
21 again, a lot of times in the FAERS report the does  
22 is not even mentioned, so that would be hard to

1 say.

2 DR. HAUSMAN: Hi, this is Ethan Hausman  
3 from DPMH. When drug development plans come to  
4 fruition and, ultimately, a drug gets approved the  
5 labeling will reference what was studied in  
6 clinical trials. If in a clinical trial a patient  
7 inadvertently got a higher dose and there happened  
8 to be an adverse event, that would -- I cannot  
9 assure, but it would almost surely be captured  
10 in case report forms and it would come in on the  
11 pre-market data. So it may be reflected in  
12 labeling, but because FDA does not control or  
13 prescribe off label use, generally, we wouldn't  
14 capture doses that were not intentionally studied  
15 in pre-market development plans. However, in  
16 eventualities where either through the 915  
17 program, which is a separate kind of safety  
18 assessment that's done after a drug is launched or  
19 through exercises like the pediatric advisory  
20 committee, if we find out later on that there's a  
21 safety issue that may have been associated with a  
22 higher than labeled drug exposure, that could find



1 its way into labeling. So it's not that it cannot  
2 happen, but as general course during drug  
3 development the way it's done now, we reference in  
4 labeling doses that were intentionally studied.

5 DR. HUDAK: Dr. Cnaan.

6 DR. CNAGN: Avital Cnaan. I just wanted  
7 to better understand what is the FDA asking us?  
8 That is it plans to monitor for epistaxis and  
9 insomnia and I assume any other sleep related and  
10 continued pharmacovigilance. These events right  
11 now are not on the label, we don't have enough  
12 information to consider adding them to the label.  
13 What are we actually voting on?

14 DR. HUDAK: Dr. Nelson.

15 DR. NELSON: This is Skip Nelson. I was  
16 actually thinking before the meeting I might ask  
17 Bob to comment on what ongoing pharmacovigilance  
18 is, because I think it -- what we're doing at this  
19 meeting and what you saw, for example, with EXJADE  
20 is not what normally happens in terms of pulling  
21 out the pediatric data and doing a pediatric focus  
22 safety review, but that doesn't mean that all of

1 the adverse events as they come in to the FDA are  
2 not looked at. They are, in fact, looked at. So  
3 maybe if Bob wants to describe what goes on within  
4 pharmacovigilance -- we used to call it routine  
5 and we got away from that word because that sort  
6 of implied we don't do alot. So we're just  
7 calling it ongoing pharmacovigilance and there's a  
8 fair amount that they do. So I don't know, Bob,  
9 if you want to comment on what actually happens,  
10 we're just suggesting we do what we normally do is  
11 what you're voting on. But, Bob --

12 DR. LEVIN: Sure.

13 DR. NELSON: -- you want to explain what  
14 that is?

15 DR. LEVIN: Getting back to your -- one  
16 of your specific questions. Our question is  
17 whether we just continue our regular, typical  
18 pharmacovigilance, otherwise known as routine.  
19 For these two adverse events, we currently don't  
20 think there's a clear case that they're drug  
21 related. And they're both actually fairly common  
22 background events in pediatric patients and

1 really, I think, that's maybe the only question we  
2 might have. If we -- I see some nods that we  
3 agree that those are common background events. So  
4 we're just asking our typical question, does the  
5 panel recommend just our usual pharmacovigilance  
6 versus something specific? And so far our plan is  
7 probably to continue with our usual  
8 pharmacovigilance. And then getting to Skip's  
9 point and you probably know, for each drug on the  
10 market we have a dedicated safety evaluator, in  
11 this case, Dr. Swank, covering that drug. She  
12 receives all reports of adverse events. And one  
13 thing we would do is just take note of whether we  
14 do see other cases of epistaxis or other bleeding  
15 events, other neuropsychiatric events. That's  
16 what we would do typically. Right now we wouldn't  
17 propose to do -- actually, I think, Kim actually  
18 has looked at whether there are similar events and  
19 we didn't see any other events consistent with  
20 bleeding, so we would, at this point, do our usual  
21 pharmacovigilance and keep on whether there are  
22 events that might suggest the causal effect.

1 DR. HUDAK: Dr. Hausman .

2 DR. HAUSMAN: Hausman. Actually, no.  
3 I'm fine.

4 DR. HUDAK: Any other comments?  
5 Questions? All right. In that case we will  
6 consider the FDA question and, specifically, that  
7 is, does the Committee agree with the  
8 recommendation for continued pharmacovigilance  
9 monitoring for this medication? And so we'll,  
10 first, have everybody press their buttons yes or  
11 no on their phones and for the two people on the  
12 phone we will hold on you since you don't have  
13 devices and get your oral votes, subsequently. We  
14 we're waiting for information to appear on the  
15 screen, but if not we will -- I guess we'll go  
16 around the room then -- nope, wait. Okay.

17 UNIDENTIFIED SPEAKER: Now, you can go  
18 around.

19 DR. HUDAK: All right. So Dr. Kishnani  
20 and Dr. Havens, do you want to vote on this?

21 DR. HAVENS: Approve. Havens.

22 DR. KISHNANI: This is Priya. Approve.

1 DR. HUDAK: Thank you. Okay. We'll go  
2 around the room. We'll start with Dr. Turer.

3 DR. TURER: I approve.

4 DR. SAYEJ: Wael Sayej. I approve.

5 DR. KASKEL: I approve. Rick Kaskel.

6 DR. ANNE: Premchand Anne. I approve.

7 DR. WADE: Kelly Wade. I approve.

8 DR. CATALETTO: Mary Cataletto. I  
9 approve.

10 DR. MOORE: Erin Moore. I approve.

11 DR. WHITE: Michael White. Agree.

12 DR. CALLAHAN: David Callahan. Yes, I  
13 approve.

14 DR. ZUPPA: Athena Zuppa. Yes, I  
15 approve.

16 DR. CNAGN: Avital Cnaan. I approve.

17 DR. HUDAK: All right. So in summary,  
18 we have a unanimous committee opinion to continue  
19 pharmacovigilance, whether it's -- whatever the  
20 name of it is, routine or otherwise. So at this  
21 point we will break. It is 10:34. We have a 15  
22 minute break, so if everybody can reconvene at

1 10:50? Does that meet everybody's satisfaction?  
2 And then we will finish out the morning session.  
3 Thank you.

4 (Recess)

5 DR. HUDAK: Assuming that our -- yes.  
6 Hold on a second. All right. Okay. I'm going to  
7 do this right this time and introduce the FDA  
8 people who are joining us for the discussion of  
9 Nitropress. So I'll come to you. But who's  
10 sitting at the table, if you can sort of identify  
11 yourselves and what you do.

12 DR. MISTRY: Kusum Mistry, Drug Use  
13 Analyst, Division of Epidemiology II.

14 DR. CHEN: Amy Chen, Safety Evaluator,  
15 Division of Pharmacovigilance, Office of  
16 Surveillance and Epidemiology.

17 DR. POPOLAN: Tom Papoian, Supervisor of  
18 Pharmacologist, Division of Cardiovascular and  
19 Renal Products.

20 DR. WORONOW: Daniel Woronow,  
21 Cardiologist, Medical Officer, Division of  
22 Pharmacovigilance I.

1 DR. DWIVEDI: Rama Dwivedi, Pharmacology  
2 Toxicology, Division of Cardio Renal Products,  
3 FDA.

4 DR. SENATORE: Good morning. Fred  
5 Senatore, Cardiologist and Medical Officer with  
6 the Division of Cardiovascular and Renal Products,  
7 OND; Office of New Drugs.

8 DR. WALDRON: Peter Waldron, Medical  
9 Officer, Division of Pharmacovigilance.

10 DR. HUDAK: And our speaker is Dr.  
11 Mulugeta; is that close?

12 DR. MULUGETA: Lily Mulugeta.

13 DR. HUDAK: Thank you. And I think  
14 eight people, I think this is a record, in terms  
15 of the representation here. So this will be an  
16 exciting topic. So why don't you start.

17 DR. MULUGETA: Thank you. Again, Lily  
18 Mulugeta, I'm a clinical reviewer in the Division  
19 of Pediatric and Maternal Health and I'll be  
20 presenting the pediatric focus safety review for  
21 Nitroprusside. This is the outline of my talk.  
22 I'll provide some background information, discuss

1 the pediatric studies and labeling changes, drug  
2 use trends, as well as adverse events for  
3 Nitroprusside. Nitroprusside was originally  
4 approved in 1981, it's a direct acting  
5 vasodilator. It's approved for multiple  
6 indications, including for immediate reduction of  
7 blood pressure and hypertensive crisis both in  
8 adult and pediatric patients. It's approved for a  
9 continuous infusion starting at a dose of 0.3  
10 microgram per kilo per minute, titrated to affect  
11 up to 10 micrograms per kilo per minute. The  
12 labeling change to include pediatric information  
13 occurred in November of 2013. Efficacy in the  
14 pediatric population was established based on data  
15 in adults, as well as two PK/PD studies in patients  
16 birth to less than 17 years of age. In these  
17 studies there were no new safety signals that were  
18 identified. And the dose that's approved in  
19 children is the same dose that's approved in  
20 adults. Just to briefly mention, since this is a  
21 drug that was approved awhile ago, pediatric  
22 studies were conducted under a written request for



1 this product. The flow chart on the right side  
2 shows the prizes for the National Institute of  
3 Health which is responsible for conducting studies  
4 for off patent drugs. I'm not going to go through  
5 the flow chart, but we thought it would be  
6 important to have it here for you. Aside from  
7 hypotension the most important toxicities of  
8 sodium nitroprusside includes cyanide toxicity,  
9 thiazide toxicity as well as methemoglobinemia.  
10 And all these are related to the disposition of  
11 the drug and are included in the product labeling.  
12 This table displays the nationally estimated  
13 number of patients with hospital discharge billing  
14 for Nitroprusside from U.S. non-federal hospitals  
15 from the date of the pediatric labeling, which I  
16 mentioned was in November of 2013 through July  
17 2016. And as you can see, out of nearly 2,000  
18 patients who received Nitroprusside during that  
19 time, approximately, 6 percent of that use was in  
20 pediatric patients. And the largest proportion of  
21 use within the pediatric patients were in infants  
22 less than 1 year of age. And just as a reminder

1 to the committee, the use data does not contain  
2 use data from special or stand-alone pediatric  
3 hospitals or other specialty hospitals. So this  
4 does not necessarily reflect the total use of  
5 Nitroprusside in the pediatric population. There  
6 were a total of 26 serious adverse reports that  
7 were identified in FAERS between 1998 and 2016 out  
8 of which 12 resulted in death. Of the 26  
9 pediatric reports, six were excluded because of  
10 duplication. So for the purpose of today's  
11 presentation I'll be focusing on the 20 adverse  
12 reports, which include eight fatalities. This is  
13 a summary of the total adverse events. As I  
14 mentioned there were eight fatal adverse events  
15 including three cases of cyanide toxicity, two  
16 cases of cardiovascular events and one case of  
17 elevation in carboxyhemoglobin level. There were  
18 also a total of non -- 12 non-fatal serious  
19 adverse events including four cases of elevation  
20 in carboxyhemoglobin level, three cases of cyanide  
21 toxicity, two cases of cardiovascular events and  
22 one case of transient blindness. In the next few

1 slides I will go over the fatal adverse events and  
2 provide high level summaries. So as I mentioned  
3 there were three cases of cyanide toxicity, these  
4 were in patients with complex congenital heart  
5 defects who had complicated and preoperative  
6 and/or post-operative course and had Cyanide  
7 levels that were reported as toxic following  
8 Nitroprusside infusion. All three patients died  
9 within a few days of their surgical repair. Based  
10 on the review of the case reports, the cause of  
11 death in all cases was likely associated with  
12 complex underlying disease, although it's not  
13 clear if cyanide toxicity could have contributed  
14 to the fatal outcome. As I mentioned earlier,  
15 cyanide toxicity is a known adverse event of  
16 Nitroprusside, it's related to its drug  
17 disposition and it's already included in the  
18 warning section of the product labeling. There  
19 were two cases of fatal cardiovascular events.  
20 The first case is a 10 month-old patient with  
21 Congenital Heart Disease who died during surgical  
22 repair. The patient received intraoperatative

1 Nitroprusside as well as dobutamine infusions.  
2 The second case is a two year-old patient with  
3 fetal alcohol syndrome who experienced hypotension  
4 after a dose of Nitroprusside was inadvertently  
5 administered. Blood pressure did normalize after  
6 the infusion was discontinued, but the patient  
7 died the following day following a series of three  
8 cardiac arrests. The cause of death in both cases  
9 was likely associated with the underlying disease,  
10 hypotension is a known adverse event of  
11 Nitroprusside and it's due to an extension of its  
12 active pharmacological properties. In the next  
13 few slides I'll discuss cases of elevation of  
14 carboxyhemoglobin levels both fatal and non-fatal.  
15 I'll talk about the potential mechanism for this  
16 effect and I'll present the Agency's assessment of  
17 these findings. So there were five cases of  
18 patients who had elevated carboxyhemoglobin  
19 levels, these level ranged from 5.3 percent to 16  
20 percent. Of the five cases there was one fatality  
21 in a four year-old with complicated underlying  
22 medical history who received a high dose of

1 Nitroprusside at 16 micrograms per kilo per minute  
2 for 12 hours. And I had mentioned earlier that  
3 the approved dose has a maximum of 10 micrograms  
4 per kilo per minute and this was due to a  
5 medication error. The rest of the patients or the  
6 other four patients had no signs or symptoms of  
7 toxicity or hemolysis and recovered without any  
8 sequelae. The table provides additional  
9 details on these cases. So there is a plausible  
10 mechanism for Nitroprusside induced elevation in  
11 carboxyhemoglobin levels. Nitroprusside is a  
12 nitric oxide donor and can induce heme oxygenase-1 (HO-  
13 releasing carbon monoxide. Carbon monoxide can  
14 then bind to hemoglobin forming carboxyhemoglobin  
15 and displacing oxygen from hemoglobin.  
16 Carboxyhemoglobin level is typically less than 2  
17 percent in non-smokers and less than 9 percent in  
18 smokers. In terms of signs and symptoms of  
19 toxicities, the symptoms vary depending on levels.  
20 Mild to moderate elevations in carboxyhemoglobin  
21 levels can present as headache or nausea and  
22 severe elevations can include -- can result in

1)

1 seizure, syncope and acidosis. In this slide I'll  
2 be presenting the Agency's assessment of these  
3 findings and we're presenting to you two different  
4 assessments, one from OSE and the other one from  
5 the Division of Cardio Renal Products. First I'll  
6 present the OSE's assessment of these findings and  
7 that includes that there was a documented temporal  
8 rise in carboxyhemoglobin levels in the five cases  
9 that I described a few minutes ago. All patients  
10 had complicated underlying disease, four were  
11 post-operative cardiac transplant patients. There  
12 was a decrease in carboxyhemoglobin level with  
13 Nitroprusside discontinuation in four cases, the  
14 four -- and the other one was that fatal case.  
15 There was no reported carboxyhemoglobin related  
16 symptoms in any of the patients. We were unable  
17 to identify additional cases in adults or children  
18 in the literature or FAERS. So based on these  
19 findings, OSC recommendation is to add increase in  
20 carboxyhemoglobin levels as a laboratory finding  
21 in pediatric patients to labeling. The Division  
22 of Cardio Renal Product has the following

1 assessment, that there is a plausible relationship  
2 between Nitroprusside exposure and elevated  
3 carboxyhemoglobin production. There are  
4 documented levels in patients in these case series  
5 were not associated with any carboxyhemoglobin  
6 related symptoms, raising uncertainty about the  
7 clinical relevance of the finding. There's a  
8 concern from the Division that a label change may  
9 result in an unwarranted clinical decision to  
10 discontinue Nitroprusside infusion. So based on  
11 these findings and these concerns the Division of  
12 Cardio Renal Products has concluded the following:  
13 the lack of correlation between carboxyhemoglobin  
14 levels and any signs of carboxyhemoglobin-related  
15 toxicities does not support a labeling change. So  
16 in conclusion, most cases included known adverse  
17 events and patients with complex underlying  
18 medical conditions. Nitroprusside exposure is  
19 associated with elevated Carboxyhemoglobin levels  
20 but of uncertain clinical relevance. So our  
21 question to the committee is then, are available  
22 data sufficient to support labeling for elevation

1 of carboxyhemoglobin level at this time? And I'll  
2 just like to acknowledge my colleagues on these  
3 slides for their contribution to this review.

4 DR. HUDAK: Thank you. So this is now  
5 open for questions and discussion. Dr. Sayej.

6 DR. SAYEJ: Just a quick question. Wael  
7 Sayej from Connecticut. On the fatal adverse  
8 event cases, the cardiovascular events number two  
9 patients on Slide 12, the second patient was  
10 describe as a two year-old with fetal alcohol  
11 syndrome, who was inadvertently administered the  
12 Nitroprusside. In the conclusion you said that  
13 the cause of death in both cases was likely  
14 associated with an underlying disease. I'm not  
15 sure how having fetal alcohol syndrome is an  
16 underlying disease process that will subject this  
17 kid to having a cardiac arrest without having any  
18 previous cardiac issues. Was there something else  
19 going on with this kid or is it --

20 DR. MULUGETA: Slide 12, please.

21 DR. HAUSMAN: I would defer that to the  
22 pharmacovigilance reviewers in relation the AERS



1 case that was discussed.

2 DR. MULUGETA: I can also comment.

3 DR. HAUSMAN: Yeah.

4 DR. MULUGETA: So the patient had  
5 sustained a cardiac arrest prior to receiving  
6 Nitroprusside infusion, after having fallen from a  
7 crib and prior to cardiac surgery. So the patient  
8 had a complicated history in addition to having  
9 fetal alcohol syndrome as well. Maybe the OSC  
10 reviewer can add additional detail if needed.

11 DR. CHEN: Amy Chen. Yes, the patient  
12 did experience cardiac arrest prior to receiving  
13 the Sodium Nitroprusside infusion, so that was a  
14 factor that we took into consideration as  
15 compounded by underlying disease.

16 DR. HUDAK: Dr. Anne.

17 DR. ANNE: In the summary of findings,  
18 you know, the big conclusion was the lack of  
19 correlation between carboxyhemoglobin levels and  
20 any signs of carboxyhemoglobin toxicity does not  
21 support a labeling change. Was there any  
22 measurements made on the -- you know, to see if

1       there was metabolic acidosis or if there's bicarb  
2       -- decrease in bicarb or any evidence of that? I  
3       know, because we're not seeing the physical  
4       symptoms but in a --

5                 DR. CHEN: Amy Chen. So in these  
6       carboxyhemoglobinemia cases, in regards to lactic  
7       acidosis or metabolic acidosis, two cases in our  
8       series describe cyanide levels, but there were  
9       normal. However, the levels were drawn at the  
10      time Sodium Nitroprusside was discontinued. The  
11      authors did not think that the cyanide levels were  
12      excessively elevated because the patients did not  
13      show any rise in lactic acid or development of  
14      metabolic acidosis.

15                DR. HuDaK: Could you summarize what you  
16      know about the actual doses of Nitroprusside  
17      administered in the cases with the elevated  
18      carboxyhemoglobin? Were the label dosing  
19      instructions being followed to the letter?

20                DR. MULUGETA: In the carboxyhemoglobin  
21      cases one patient received a dose outside the  
22      recommended dosage which was 16 micrograms per kg

1 per minute. The recommended labeling dose for  
2 Sodium Nitroprusside is .3 to 10 mics per kilo per  
3 minute. If we can go to Slide 13 we have a table  
4 that summarizes all the doses. So other than the  
5 4 year-old who received the inadvertent  
6 administration that exceeded the recommended dose,  
7 all the other doses were within the recommended  
8 range, but some of them were definitely on the  
9 higher side.

10 DR. HuDaK: So I'd be interested in what  
11 the cardiologists in the room think about this,  
12 but the label dose says, dose may be increased to  
13 10 micrograms per kilogram per minute but for no  
14 longer than 10 minutes, I think. At least in my  
15 practice doses of 8 micrograms per kilogram per  
16 minute if given over a long period of time are  
17 high. Dr. White.

18 DR. WHITE: I was just rubbing my head.  
19 I don't think the data is very clear that  
20 carboxyhemoglobin is a problem. I mean, we've got  
21 14,000 cases and then the ones that it was metered  
22 in, there were four transplant patients where they

1 followed it pretty closely and that's where all  
2 the data comes -- most of the data comes from.  
3 And without any data to suggest that there were  
4 clinical symptoms associated with the measured  
5 level of carboxyhemoglobin -- and I think all the  
6 carboxyhemoglobin levels that were measured are  
7 well below, let's see, there's a list of where you  
8 should see symptoms in the pharmacology summary on  
9 Table 2. Percentage carboxyhemoglobin levels in  
10 symptomatology and obviously, this is not an  
11 inference, but 10 percent asymptomatic; 20 percent  
12 dizzy and nausea and syncope; 30 percent  
13 carboxyhemoglobin, visual disturbances; 40 percent  
14 confusion and syncope; 50 percent seizures and  
15 coma and none of the levels that were mentioned  
16 were anywhere close to those levels where at least  
17 in older people where you can get some measure of  
18 symptomatology, you would be symptomatic. Now the  
19 pharmacology also reviews the data that seems to  
20 be emerging that cellular c.o. may serve as  
21 intracellular messenger system similar to nitric  
22 oxide and maybe there's something happening at the

1 intracellular level that's different that might  
2 produce toxicity that we can't measure in any way  
3 with our current data. But I think I would agree  
4 with the conclusions of the FDA, that we don't  
5 have enough data to proceed yet. But I think we  
6 need to have a high level of vigilance looking at  
7 what may be emerging as a signal. And just from  
8 my experience as a pediatric cardiologist back  
9 when it wasn't labeled for kids in the dark ages,  
10 we used it at very high levels for very prolonged  
11 periods of time, both looking -- without even  
12 monitoring for the cyanide toxicity and we rarely,  
13 rarely, rarely had to discontinue it for any  
14 symptoms the patients were having. But that's  
15 just antidotal, it doesn't mean anything.

16 DR. HUDAK: Okay --

17 DR. WALDRON: Doctor, may I make a  
18 comment to Dr. White?

19 DR. HUDAK: Yes.

20 DR. WALDRON: Peter Waldron, DPV. We  
21 were concerned about a few things. One is that  
22 the -- all the data that I saw and looking at the

1 clinical pharmacologist and toxicologist review  
2 was in adults.

3 DR. WHITE: Yes.

4 DR. WALDRON: And so what we don't know  
5 -- I don't think we know much about the symptom  
6 levels relative -- or the symptom manifestation  
7 relative to the carboxyhemoglobin levels. So  
8 that's one. Two is that the -- I was concerned  
9 that although the carboxyhemoglobin levels as you  
10 just described level and symptom is important.  
11 What I didn't know before entering into this was  
12 the avidity of myoglobin and specifically,  
13 cardiomyocyte myoglobin, which is, I think I'm correct  
14 in saying three times greater than the avidity of  
15 hemoglobin for carbon monoxide. There's just some  
16 real uncertainty about what blood levels even  
17 represent with regard to what may be a more  
18 vulnerable population who are undergoing cardiac  
19 surgery and certainly their hearts are already at  
20 stress. And the third point is that I did talk to  
21 a friend who is a cardiac anesthesiologist -- a  
22 pediatric cardiac anesthesiologist and he was

1       saying that they don't routinely get  
2       carboxyhemoglobin levels as part of preoperative  
3       arterial blood cast monitoring. So it's available  
4       in any institution that's going to be doing  
5       cardiothoracic surgery, but it's not part of the  
6       routine readout for monitoring that context. And  
7       so we had some concern that although there were  
8       not cases, that were also possibly not looking and  
9       so, again, uncertainty about the under  
10      ascertainment.

11                 DR. WHITE: If I may respond to that? I  
12      would say that a, we don't routinely monitor  
13      carboxyhemoglobin. Too, a lot of the infants are  
14      newborn surgery, neonatal surgery and would have  
15      fetal hemoglobin floating around and I doubt that  
16      we have good data to tell us what the effects on  
17      fetal hemoglobin might be or how that interaction  
18      might play. I mean, there are so many questions  
19      that need to be answered, I think we need to  
20      answer the questions before we put out a general  
21      warning or any sort of statement that we actually  
22      have an idea of what we're doing.

1 DR. HUDAK: Dr. Nelson.

2 DR. NELSON: Yes. This is Skip Nelson.  
3 Just want a clarification. Could you go to Slide  
4 15? And this is just a correction to your  
5 comment, Michael about FDA conclusion. I just  
6 want to point out there's two --

7 DR. WHITE: I'm sorry.

8 DR. NELSON: -- two conclusions on the  
9 table and we're asking you to discuss and choose.

10 DR. WHITE: I can't read that.

11 DR. HUDAK: All right. While he's  
12 reading that, Dr. Zuppa and then Dr. Havens, on  
13 the phone, have questions.

14 DR. ZUPPA: I think -- and so -- I'm a  
15 pediatric ICU doc and we actually use the COHb in  
16 the ICU setting as well, not just in cardiac  
17 surgery or other cardiac population. I think that  
18 the choices we have in certain situations are not  
19 necessarily increasing unless we have a  
20 hypertensive emergency. We can go to nicardipine  
21 or nipride. Nicardipine has effects on the  
22 myocardium or the nipride does. So I would just



1 be reluctant to put out warnings or -- if there  
2 not, I guess, for sure is the right way to put it.  
3 But I think -- we actually do monitor for  
4 carboxyhemoglobin, that Hemoglobin in the ICU with  
5 blood gas sampling. So I don't know if -- but  
6 what you said about the cardiac myoglobin, I never  
7 knew that. So maybe, I don't know, educating  
8 would be more appropriate and recommendations for  
9 increased monitoring and why it's important might  
10 be a way to go. I don't know if that makes sense.

11 DR. HUDAK: Dr. Havens.

12 DR. HAVENS: Thank you very much. So  
13 I'm glad that you brought this slide up, that OSC  
14 says they want -- that there is an association  
15 with an increase in carboxyhemoglobin and it  
16 sounds like the DCRP agrees with that, but doesn't  
17 understand the clinical implication. So they're  
18 recommending to not change the label identifying  
19 the association. Do I understand that right? Do  
20 they both agree that there is an association?

21 DR. LEVIN: Yes. That's what we -- yes,  
22 we all agree there's an association and the Cardio

1 Renal prefers not to add the information to  
2 labeling. And one more point, I think overall --

3 UNIDENTIFIED SPEAKER: Can you identify  
4 yourself?

5 DR. LEVIN: I'm sorry. Bob Levin from  
6 FDA. Another point is most likely -- so far none  
7 of us really are suggesting a warning. So far  
8 that's been the case, that we're primarily  
9 thinking to put the information as a laboratory  
10 finding, again, acknowledging that we're not clear  
11 about what the clinical significance could be.  
12 And it probably, at this point, wouldn't rise to  
13 the level of a warning, but that's -- people might  
14 have a different opinion about that.

15 DR. PAPOIAN: Tom Papoian. Just for  
16 clarification that the Division does not disagree  
17 with adding something to the label to designate a  
18 laboratory finding. The original conclusion and  
19 recommendation was that this was a safety finding  
20 that was considered an adverse of that and our  
21 recommendation was addressing that issue.  
22 Subsequent to that OSE modified the recommendation

1 to make it a lab finding and we didn't get a  
2 chance to agree or disagree with that and so I  
3 think our recommendations are still based on the  
4 original level of safety issue and the relevance  
5 of that safety issue for the label.

6 DR. HAVENS: And so now OSC and DCRP  
7 agree that there is a laboratory finding  
8 associated with use of the drug and it's not  
9 unreasonable to put it into the label as a  
10 laboratory finding; is that right?

11 DR. PAPOIAN: Tom Popolan again. I  
12 think there's multiple points of view on whether  
13 we agree or disagree with putting something in the  
14 laboratory finding, but what's on the slide now  
15 was not regarding the laboratory finding, it had  
16 to do with whether this was a true safety finding,  
17 because there was no actual clinical consequence.  
18 The authors of the original paper had -- the dosed  
19 this drug for several days, they didn't state any  
20 clinical consequence so we weren't sure if this  
21 rose to the level of an adverse effect. But we  
22 don't have a firm conclusion on whether we

1 disagree with including it as a laboratory  
2 finding, that's still an open question.

3 DR. HUDAK: Okay. Dr. Callahan and then  
4 Dr. White.

5 DR. CALLAHAN: David Callahan. I think  
6 adding the information is useful information as  
7 stated in the summary slide that Nitroprusside  
8 exposure is associated with elevated  
9 carboxyhemoglobin levels of an uncertain clinical  
10 relevance. I think that's helpful information to  
11 have on the label.

12 DR. WHITE: Can you -- I'm kind of slow  
13 some days. It looks like most of the data that we  
14 have is from a transplant study -- four post  
15 transplant hearts. Is that -- is that where most  
16 of the data we have is coming from? Is that  
17 correct?

18 DR. CHEN: Yes.

19 DR. WHITE: It seems to me that a post  
20 transplant heart is very different from anybody  
21 else's heart in many ways. And the post  
22 transplant physiology is very different in many

1       ways. We're doing a lot of immunosuppression,  
2       we're doing other things that we don't typically  
3       do in most patients. And there also seems to be  
4       some association at the intracellular level  
5       between nitric oxide and Nitroprusside in  
6       potential interactions there that might also be  
7       affecting the levels that we see. I'm not sure  
8       that we can generalize data from post transplant  
9       patients to just general patients -- the  
10      physiology in normal non-transplant patients. Do  
11      we have any way of acquiring a good data base from  
12      other subjects?

13                 DR. DWIVEDI: So I do -- I agree that  
14      this data is coming mainly from this heart  
15      transplant patients, nothing -- no other data is  
16      available.

17                 UNIDENTIFIED SPEAKER: Please identify  
18      yourself.

19                 DR. DWIVEDI: This is Rama Dwivedi from  
20      Cardio Toxicology, Division of Cardiology and  
21      Renal Products, FDA.

22                 DR. HUDAK: Dr. Cnaan.

1 DR. CNAAN: This is the data only on  
2 cardio post- transplant patients, is that what  
3 should be in the label in some form? Because that  
4 is a population that might get this treatment and  
5 the warnings should be for them or --

6 DR. WHITE: It's one paper with four  
7 subjects.

8 DR. DWIVEDI: That's correct.

9 DR. HUDAK: Dr. Havens has a follow-up?

10 DR. HAVENS: Yeah. So it gets to the  
11 same point here, that it's one paper with four  
12 subjects in Spain and published in 2005, so it  
13 seems like since it's been in the public realm for  
14 so long, there might have been other reports if  
15 this were an issue that people seem to be  
16 concerned about. Have there been other published  
17 reports on this topic since that 2005 paper?

18 DR. CHEN: There were no new cases  
19 identified in the literature or FAERS since 2005.

20 DR. HUDAK: Doctor.

21 DR. HAVENS: So --

22 DR. HUDAK: I'm sorry.

1 DR. HAVENS: So then -- thinking that  
2 these are really perhaps very special cases would  
3 argue it seems against a broad inclusion for  
4 everyone.

5 DR. HUDAK: So -- we have -- I think Dr.  
6 Kishnani has a question and then I have a comment.

7 DR. KISHNANI: So, mine now became a  
8 comment because I had the same question; was there  
9 any report since the original publication with the  
10 four subjects, which was in 2005. To me this just  
11 seems like this is more than a decade later and  
12 nothing has come out from this? So while it's  
13 important, I'm still not convinced that this is --  
14 this warrants a label change or an addition to the  
15 label at this time. It just doesn't seem enough  
16 information or it said like in one study, it needs  
17 to be categorized quit carefully in the transplant  
18 setting.

19 DR. HUDAK: This is Dr. Hudak. My  
20 comment on this is that I -- the issue is  
21 arboxyhemoglobinemia and whether you're a cardiac  
22 transplant patient or you're a post Norwood

1 procedure patient or whatever, there's no good  
2 rational that I could think of physiologically to  
3 say why those patients would be at differential  
4 risk for levels of carboxyhemoglobinemia, number  
5 one. Number two, the argument that may have  
6 different susceptibility, perhaps, to the same  
7 level given with your heart transplantation or  
8 something else is possible, I presume, but we  
9 don't have any evidence that there was an adverse  
10 event in that population. So baring, which I find  
11 hard to believe actually, baring that there's any  
12 data on non-cardiac transplant patients and  
13 carboxyhemoglobinemia considering that you monitor  
14 it as a standard of care in your practice is quite  
15 interesting.

16 DR. CHEN: Amy Chen from the Office of  
17 Surveillance in Epidemiology. We'd just like to  
18 bring up the point that there are many factors  
19 that affect the reporting patterns of adverse  
20 events. First of all, the reporting is voluntary,  
21 so under reporting can occur. Other factors  
22 include the length of time the product has been on



1 the market as well as the type of patient  
2 population that's being treated. So, some  
3 possible reasons for under reporting of the  
4 carboxyhemoglobinemia with Sodium Nitroprusside  
5 includes the age of the drug, the use in  
6 critically ill patient population, for example, if  
7 a patient had complicated underlying disease it is  
8 possible that the practitioner would attribute the  
9 adverse event to underlying disease versus the  
10 suspect drug. And, thirdly, we want to point out  
11 that carboxyhemoglobinemia is a rarely reported  
12 event in the FAERS database. There were very few  
13 drugs that reported this event of which Sodium  
14 Nitroprusside was the number one drug reporting  
15 this event in FAERS. And then, lastly, the  
16 potential under detection of arboxyhemoglobinemia  
17 in the clinical setting, so for example,  
18 Carboxyhemoglobin as Dr. Waldron previously stated  
19 is not usually part of an arterial blood gas  
20 profile in the preoperative setting, so one would  
21 need to specifically request for this measurement  
22 if there's a suspicion of carbon monoxide toxicity

1 and if the carbon monoxide levels are not  
2 routinely monitored then there would be a lack of  
3 an awareness of a potential drug event  
4 association.

5 DR. HUDAK: Any further comment before  
6 we vote on something? Dr. Nelson.

7 DR. NELSON: So Mark, let me help  
8 perhaps give you some clarity around the vote. So  
9 we, specifically -- I mean, the question is worded  
10 the way the question is worded and I've heard some  
11 people say maybe yes, maybe no to that. I mean,  
12 you all can vote on whether or not you think the  
13 information ought to be in the label. We,  
14 specifically, did not ask you if you think it  
15 ought to be in the label, where to put it, because  
16 we thought that was getting a bit too far into the  
17 weeds. But I think it's fair to say in agreeing  
18 with Bob, no one is thinking of this as a warning  
19 if you think of our labeling and warnings and  
20 precautions and -- nobody's thinking of it at that  
21 level it would be framed somewhere in the adverse  
22 events section in some appropriate way. So, I

1 think, you know depending on the vote -- if the  
2 vote's

3 -- you know, I mean, we could have maybe  
4 a little bit more discussion about that, but --  
5 about whether or not -- about what that might look  
6 like if it is done, but that's -- we,  
7 specifically, worded the question here as it is.  
8 Do you think it's worth putting in the label in  
9 any way shape or form? Yes or no? If the answer  
10 is yes, then, obviously, we can sort out what that  
11 might mean. But we didn't want to really go there  
12 because we thought that was a bit too in the  
13 weeds. Does that help?

14 DR. HUDAK: Responses to that?

15 DR. HAVENS: Peter Havens. I have a  
16 question.

17 DR. HUDAK: Go ahead, Peter.

18 DR. HAVENS: So when you say labeling  
19 for elevation, we're not going to recommend  
20 monitoring, we're just going to say that  
21 Nitroprusside has been associated with elevation  
22 of carboxyhemoglobin. Is that what you're talking

1 about?

2 DR. NELSON: Skip Nelson. There's been  
3 no discussion about monitoring. I don't -- I  
4 don't want to -- I mean, I could give you my  
5 personnel opinion, but I don't know if that's  
6 really appropriate. But, no, we've not had any  
7 discussion about whether we put in the label,  
8 monitoring. I think that would be more of a  
9 medical practice issue, frankly.

10 DR. HAVENS: Thank you.

11 DR. HUDAK: Dr. Zuppa.

12 DR. ZUPPA: Is the risk of ethemoglobin  
13 in the label? Because, honestly, that's what we  
14 monitor for more commonly, we send a blood gas  
15 profile, it's a coax and on that you get all the  
16 forms of hemoglobin, you get carboxyhemoglobin,  
17 methemoglobin.

18 DR. MULUGETA: It's in the label  
19 already.

20 DR. NELSON: Three paragraphs.

21 DR. ZUPPA: So the blood test that  
22 monitors for methemoglobin is the same blood test

1 that would monitor for carboxyhemoglobin, at least  
2 at our institution, but I would think that's how  
3 it is in other places with a Coax.

4 DR. HUDAK: Dr. White?

5 DR. WHITE: Just one last comment.  
6 Going through that report from Spain, I think all  
7 -- at least three of those patients were on  
8 concurrent nitric oxide, which contributes at  
9 least to the proposed mechanism for the difficulty  
10 and if we use those three or subtract those three  
11 -- I'm sorry, I didn't look at the one that was  
12 fatal, I think that patient was on nitric as well.  
13 It doesn't clarify the issue of carboxyhemoglobin  
14 in the absence of concurrent nitric oxide therapy.  
15 And I'm not sure we're not conflating two  
16 different questions and I'm not sure how to sort  
17 it out.

18 DR. MULUGETA: So three out of the four  
19 patients were on nitric oxide, the fatal -- the  
20 patient who had the fatality was not on nitric  
21 oxide.

22 DR. WHITE: I'm sorry. She was the one

1 that received twice the regular dose?

2 DR. MULUGETA: Exactly.

3 DR. WHITE: So she was -- toxicity is  
4 secondary to inappropriate dosing.

5 DR. PAPOIAN: Tom Papoian, Cardio Renal  
6 Drugs. Yeah, we also review nitric oxide as a  
7 therapy. And Nitric Oxide has a very short half  
8 life and is given by inhalation and it generally  
9 is bound up immediately by hemoglobin in the lung  
10 or other proteins before even gets to the systemic  
11 circulation. I think the authors may have missed  
12 that aspect of it and it is probably unlikely  
13 contribute much to the carboxyhemoglobin levels in  
14 the blood the way Nitroprusside would.

15 DR. HUDAK: One of the things that would  
16 be, I think, informative would be to have some  
17 idea about the dose response, with respect to this  
18 drug and carboxyhemoglobinemia. And, you know, we  
19 have some patients who are on rather high doses  
20 who had levels that were, you know, less than 10  
21 percent, except for the one patient who was on a  
22 relatively high dose, whatever that is, for four

1 days. And those are levels that are below, you  
2 know, what Dr. White quoted as the  
3 percent where you begin to experience  
4 some signs or symptoms. So, you know, with four  
5 cases with these doses, I'm not sure that we have  
6 enough information really to be helpful to people.

7 DR. HUDAK: Dr. Zuppa.

8 DR. ZUPPA: Hi. It's Athena Zuppa. I  
9 mean, this data does exist, right? So in the ICU  
10 setting where we do monitor for Methemoglobin,  
11 you're going to have a carboxyhemoglobin on the  
12 value, so it would take some partnering with some  
13 institutions that use it in the ICU or the Cardiac  
14 ICU setting. And looking back at the lab values  
15 for the -- so you're going to have monitoring for  
16 methemoglobin and with that you'll have the  
17 carboxyhemoglobin level. So the data's out there.

18 DR. HUDAK: What I'm suggesting is --  
19 this is Dr. Hudak. What I'm suggesting is, if  
20 you're using this drug at a dose of one to two  
21 micrograms per kilogram per minute, I mean, I  
22 don't know that that particular dose is going to

1 cause any perturbation in carboxyhemoglobin or  
2 not. So I agree with you, I think the data  
3 probably do exist and it would be before putting a  
4 blind statement in the label somewhere about it  
5 causing this affect, it would be nice to have some  
6 better information about dose response. I see no  
7 other hands going up. Dr. Havens, Dr. Kishnani,  
8 any questions further from --

9 DR. KISHNANI: No.

10 DR. HAVENS: No. Thank you.

11 DR. HUDAK: Okay.

12 DR. KISHNANI: Thank you.

13 DR. HUDAK: So we are going to bring up  
14 the slide on the voting question. So the question  
15 here is very simply -- we'll go with the question  
16 as it's written. Are the available data  
17 sufficient to support labeling for elevation of  
18 carboxyhemoglobin level in some section, but not a  
19 warning precaution, et cetera or section of the  
20 label at this time. So we'll vote electronically  
21 and after that's done we will start with the oral  
22 vote with Dr. Kishnani and Dr. Havens. Okay.



1 We'll start with Dr. Havens and Dr. Kishnani.

2 DR. HAVENS: Peter Havens. No. Data  
3 are not sufficient.

4 DR. KISHNANI: I agree. Data not  
5 sufficient.

6 DR. HUDAK: Okay. And then we'll start  
7 this time with Dr. Cnaan and go around the table.

8 DR. CNAAN: Data not sufficient. No.

9 DR. ZUPPA: Data not sufficient. No.

10 DR. CALLAHAN: Dr. Callahan. Yes.

11 DR. WHITE: Michael White. No. But I  
12 would like to ask that we contact some of the  
13 children's hospital ICU's and see if we can get  
14 someone to track data for us and get the data.

15 DR. MOORE: Erin Moore. No.

16 DR. CATALETTO: Mary Cataletto. No.

17 DR. WADE: Kelly Wade. No.

18 DR. ANNE: Premchand Anne. No.

19 DR. KASKEL: Rick Kaskel. No.

20 DR. SAYEJ: Wael Sayej. No.

21 DR. TURER: Christy Turer. No.

22 DR. HUDAK: Dr. Nelson.

1 DR. NELSON: Thank you Mark. We can  
2 take the voting slide down at the moment. It  
3 occurred to us as we looked at this, the next  
4 question is, that we normally ask -- is going to  
5 our -- not routine, but our standard  
6 pharmacovigilance. And so we do want to have some  
7 insight there. People have talked about possible  
8 other data sources. I might point out though is  
9 you're outside of standard pharmacovigilance which  
10 is a review of the adverse events and if we don't  
11 think that's going to be very helpful, we can  
12 certainly take suggestions about what we might be  
13 able to do, but we don't have any mechanism as  
14 opposed to some sort of a contracting mechanism to  
15 go out and ask children's hospitals, for example,  
16 to look for and give us the data on  
17 carboxyhemoglobin and Nitroprusside. But I  
18 suspect many institutions with electronic medical  
19 records ought to be very easily correlate the  
20 blood gases with Nitroprusside and maybe that's  
21 simple for someone to do with a large children's  
22 hospital that has many patients in it who might be

1 on Nitroprusside, hint, hint, hint. But anyway,  
2 so we should ask -- it's not on the slide, but we  
3 should ask for a vote on the question of our, you  
4 know, standard pharmacovigilance in continuing  
5 that separate from whether we can explore other  
6 data source to look at this avenue, which we'll  
7 certainly talk about internal and see if there  
8 are, but that would be outside of what OSC could  
9 do with FAERS data. Does that make sense?

10 DR. HUDAK: Dr. White, can you recommend  
11 some alteration in standard pharmacovigilance that  
12 might get at this question?

13 MR. WHITE: The alteration -- not  
14 really, I mean, we would have to go out and ask  
15 for data, which is really a contracting mechanism  
16 and, you know, that would be a matter of working  
17 with OSE and OPT and the Division to see if  
18 there's any way we could get those data. It would  
19 be issuing a call for those data. So there's no  
20 -- I mean -- you can recommend that, but it's not  
21 incompatible with recommending that to say we  
22 would continue our pharmacovigilance as well, I

1       guess, is what I'm saying. And I don't know in  
2       today's budget climate how easy it would be to get  
3       such a contract or how much money someone would  
4       ask for in order to do that.

5                 DR. HUDAK: You don't think you'd get  
6       volunteers?

7                 DR. WHITE: Happy to entertain that, but  
8       I don't think we can ask people to do government  
9       work for free, I think that's actually against the  
10      law.

11                DR. HUDAK: Okay. All right. We have  
12      --

13                DR. PAPOIAN: Just that Dr. Nelson did  
14      say that it's outside the scope of the discussion  
15      as far as how to obtain the data, but such studies  
16      can easily be done in animals and I'm not sure  
17      what data there is available on that, probably  
18      very little. And so we have mechanisms within the  
19      FDA to do such studies, just something to  
20      consider.

21                DR. HUDAK: Dr. Wade.

22                DR. WADE: I would just add that this

1 sounds like really useful information to us and I  
2 completely agree with Dr. Zuppa that in large  
3 freestanding children's hospitals we can link our  
4 medication records and our laboratory studies.  
5 And I don't think that there's a national database  
6 that's going to have this level of laboratory  
7 detail. So I think that that probably is your  
8 source. There's quite a bit of Nitroprusside use.  
9 We also out of such a study would get drug  
10 utilization in free standing children's hospitals  
11 since it was pointed out that that utilization in  
12 the current data structures does not include most  
13 free standing children's hospitals. So I think we  
14 could get drug utilization in such a study. We  
15 could get it to link to laboratory findings  
16 including carboxyhemoglobin and methemoglobin.  
17 But we also could get at the frequency with which  
18 surveillance is actually happening in variation  
19 across centers in terms of surveillance that may  
20 be happening on a hospital basis. So I think  
21 there's many -- there's a lot of very useful  
22 information that could be obtained from such a

1 study.

2 DR. HUDAK: Dr. Zuppa.

3 DR. ZUPPA: Hi, it's Athena Zuppa. The  
4 other interesting question too, I don't know if  
5 it's actually does or duration of exposure too.  
6 So if you get a high dose for 30 minutes versus a  
7 lower dose for three days, you know, is there a  
8 differential in risk with that? So not only can  
9 we look at convads, but we could look at doses of  
10 the drug and duration of the drug across  
11 disciplines. So in the preoperative period, in  
12 the ICU setting and see if there's differential in  
13 monitoring across disciplines as well.

14 DR. HUDAK: Dr. White, can you frame a  
15 question for us?

16 DR. WHITE: I was just about to do that.  
17 So the question that we will vote on at this time  
18 would be, recommendation -- let's see -- the  
19 question would be, in addition to standard  
20 pharmacovigilance for Nitropress, do you support  
21 FDA's efforts to obtain additional information  
22 from pediatric ICU's and CVICU's on a dose --

1 dosage duration relationship to  
2 carboxyhemoglobinemia?

3 DR. HUDAK: So we'll start with Dr.  
4 Havens and Dr. Kishnani.

5 Sorry.

6 DR. HAVENS: It sounds to me like that's  
7 a two --

8 DR. HUDAK: We'll do the electronic vote  
9 here and then we'll come back to you two.

10 DR. HAVENS: Is this a two-part  
11 question?

12 DR. HUDAK: No, it's a one-part  
13 question. I will repeat it.

14 DR. NELSON: Mark, can I make a  
15 suggestion? Just separate the question of doing  
16 anything in addition from the question of our  
17 usual pharmacovigilance. That way Peter's concern  
18 is eliminated. And I don't think we -- I'll just  
19 put on the table, I don't think we necessarily  
20 need a vote on trying to sort out a way to get  
21 these data elsewhere. I mean, if people want to  
22 when they specify their comments say whether they

1 think that's worth doing, we can take that as a  
2 reasonable view. It won't add more force to know  
3 that everybody voted versus everybody said it's a  
4 good idea. So I would just vote on the  
5 pharmacovigilance question as a clean question and  
6 then in people's comments, they could comment on  
7 whether they think we should explore avenues. And  
8 I might say, this was a BPCA study, so that's also  
9 another mechanism is to see if we can partner with  
10 an ICHD to ask for these data as well. There's  
11 different ways that we can try and approach that.

12 DR. HUDAK: Okay. So we will vote on  
13 the question strictly of then doing, does the  
14 committee recommend that FDA continue standard  
15 pharmacovigilance first? Vote on that and then in  
16 the discussion period elaborate.

17 Okay. We'll start with the orals with  
18 Dr. Havens and Dr. Kishnani.

19 DR. KISHNANI: This is Priya. I agree.

20 DR. HAVENS: Peter Havens. I support  
21 standard pharmacovigilance and support a further  
22 study.



1 DR. HUDAK: Dr. Turer.

2 DR. TURER: Christy Turer. I support  
3 routine pharmacovigilance and agree with obtaining  
4 further data.

5 DR. SAYEJ: Wael Sayej. I support  
6 continued pharmacovigilance and to collect further  
7 data.

8 DR. KASKEL: Rick Kaskel. I support  
9 further vigilance and follow up with some  
10 additional data.

11 DR. ANNE: Premchand Anne. Support  
12 vigilance and obtaining further data.

13 DR. WADE: Kelly Wade. I agree with the  
14 ongoing work and support further efforts to  
15 acquire more data.

16 DR. CATALETTO: Mary Cataletto. I  
17 support routine pharmacovigilance and the  
18 exploration of opportunities to get further data  
19 on this topic.

20 DR. MOORE: Erin Moore. I support the  
21 continued vigilance and also the suggestion to  
22 collect more data.

1 DR. WHITE: Michael White. I agree with  
2 the ongoing surveillance and would suggest efforts  
3 by the FDA and pediatric advisory committee to  
4 seek some clarification of this issue,  
5 particularly in infants under a year of age, which  
6 may present a separate population from children at  
7 older ages and adults.

8 DR. CALLAHAN: David Callahan. Yes.

9 DR. ZUPPA: Athena Zuppa. Yes. And I  
10 support getting the data. I'd be happy to  
11 collaborate with the FDA to do so.

12 DR. CNAAN: Avital Cnaan. Yes. And  
13 support getting additional data.

14 DR. HUDAK: Dr. Nelson.

15 DR. NELSON: I just want to summarize in  
16 my own mind the sort of avenues we can pursue in  
17 that. I mean, one mechanism is sorting out within  
18 FDA whether we can contract for those data.  
19 That's complex and may not be the easiest thing to  
20 do. The other was the mention about doing animal  
21 studies, whether that's partnering with NCTR or  
22 the like, I mean, we could figure out if there's

1 ways to do that. The third might be to -- since  
2 this was Nitroprusside was done under BPCA, as I  
3 recall, we could then talk with an ICHD whether  
4 the pediatric trial network could gather up some  
5 of these data and the like. So we'll pursue some  
6 of those options and see what we can sort out on  
7 this issue. It doesn't strike me that it would be  
8 that hard once we get the mechanism down, but the  
9 mechanism might be hard. But, thank you for the  
10 comments.

11 DR. HUDAK: Okay. So in summary, the  
12 committee has almost unanimously decide that  
13 available data are not sufficient at this time to  
14 support labeling for carboxyhemoglobinemia. They  
15 do support unanimously standard pharmacovigilance  
16 and have requested FDA to explore other methods to  
17 obtain additional data. So with that we are at  
18 the end of the morning session. We are a little  
19 bit early. We will reconvene at 1:00. Thank you.

20 (Recess)

21 DR. HUDAK: 1:03 p.m., most people are  
22 here, a few stragglers. All right, so the

1       afternoon program is devoted to pharmacogenomics.  
2       It's a topic, I think, that was developed perhaps  
3       in large part after discussion at our earlier  
4       meeting with respect to one of the HIV medications  
5       and I think, Skip, you said you've put something  
6       together so thank you. So, you can introduce.

7                 DR. NELSON: Thank you, Mark. So --  
8       okay, cool. So yes, the role of pharmacogenomic  
9       data and pediatric therapeutics. So as Mark  
10      mentioned, this is a rise -- the topic arose out  
11      of our discussion at the September 2016 Pediatric  
12      Advisory Committee Meeting where Sustiva or  
13      Efavirenz was discussed and in that context, you  
14      all discussed the role of therapeutic drug levels,  
15      the risks of rapid metabolizers, how  
16      pharmacogenomic testing may be useful and whether  
17      this information should be added to labeling and  
18      rather than sort of target that one drug for  
19      discussion at that point, we suggested that we  
20      have a more general discussion on the role of  
21      pharmacogenomics in pediatric drug development and  
22      in the clinical use and labeling of these

1 products.

2 I mean just note to give you some  
3 context that during the PAC discussion, and I hope  
4 that if I don't have this correct, Peter will  
5 correct me from the phone but it was noted that  
6 the recommendations of this panel and  
7 antiretroviral therapy and medical management of  
8 HIV infected children, huge document, you were all  
9 there, recommends that Efavirenz generally not be  
10 used in children less than three years of age and  
11 if it's unavoidable due to the clinical situation  
12 that what was called investigational doses, which  
13 by that I assume meant off label uses of this  
14 medication were suggested and it gave some  
15 recommendations for that dose and we don't  
16 necessarily have to go into today but I also noted  
17 that the suggested evaluation of the CYP2B6  
18 genotype would be required prior to use so that's  
19 -- and there was some discussion of that at the  
20 September 2016 advisory committee so rather than  
21 have that drug be the reason for the discussion at  
22 that time, given that it happened to be the one on

1 the docket. We suggested a broader discussion of  
2 this topic and to try and set this up for you, we  
3 have four presentations.

4 I am not even going to great detail  
5 about what the presentations are and I'll let each  
6 individual who is presenting to introduce  
7 themselves but we thought we would start with  
8 pharmacogenomics and pediatric drug development  
9 and labeling. Dionna Green will present that and  
10 then Mike Pacanowski will present some case  
11 studies on pharmacogenomics. Kellie Kelm will then  
12 present some information about analytical and  
13 clinical validation of pharmacogenomic tests  
14 because obviously if you are going to use a drug  
15 based on a test, you need to have some  
16 understanding of the test.

17 And then we've asked Steve Leeder from  
18 Children's Mercy to talk about the clinical  
19 implications of the use of pharmacogenomic testing  
20 in children. We thought that would be a nice sort  
21 of way to set up a discussion. Now, we chose four  
22 examples and we did this for two reasons, one is

1 we tried to pick examples that reflected a range  
2 of different issues. So Steve, CYP3A, CYP2B6 I can  
3 read, Athena certainly knows what those are, Steve  
4 will.

5 Depakene is a contraindication based on  
6 mutations in mutations on POLG mitochondrial DNA  
7 polymerase gamma. Strattera or atomoxetine, the  
8 root of elimination is CYP2D6 and then Plavix,  
9 clopidogrel is a pro drug activated by multiple  
10 CYP450 enzymes including CYP2C19 and so what we  
11 tried to do is pick four drugs that had a range of  
12 issues, all of which were slightly different  
13 issues and different enzymes. Why did we do that?

14 We did that so we could screen you all  
15 for conflict of interest around these four drugs  
16 so there is no constraint about using these as  
17 examples in the context of pharmacogenomics.  
18 That's important because we don't -- there may be  
19 other drugs that can illustrate a point but we've  
20 not cleared everybody around conflict of interest  
21 on those other drugs and so the preference would  
22 be to limit the conversation about the important

1 of pharmacogenomics to these four products so we  
2 don't have to worry about who may or may not be  
3 conflicted around those other drugs.

4           You'll see other drugs in the  
5 presentations because sometimes it might  
6 illustrate a point and there is a publication that  
7 Dionna will mention which has tables in it of  
8 other drugs but that's the purpose of these four  
9 drugs, to allow for a robust discussion without  
10 any concern about using it and to give board  
11 enough examples of the issues that are under  
12 discussion.

13           We then proposed two discussion topics  
14 and you'll see these at the end as well. Again,  
15 this is a non-voting discussion but discussion  
16 one, we wanted to focus on what's the role of  
17 pharmacogenomic testing in your care of patients  
18 and we suggest some topics to consider as you are  
19 discussing that issue although there may be other  
20 topics that you think are important around the  
21 role of pharmacogenomic testing so these topics  
22 are meant to be ways of stimulating discussion,



1 not to say you have to limit yourself to those  
2 topics but what are the situations where you would  
3 order it before prescribing, what are the  
4 challenges that may arise in ordering it? And we  
5 are being vague around those challenges but  
6 whatever challenges you find in the clinic, in  
7 ordering it, its availability or whatever, and  
8 then what are the situations where you might  
9 request a pharmacogenomic test to explore in  
10 association with an adverse event that is  
11 experienced by your patient so after the fact and  
12 then what kind of sources of information would you  
13 use to inform your use of pharmacogenomic  
14 information in your clinical practice. So the idea  
15 is how do you use this in the clinic, what are the  
16 challenges, what are the situations and then what  
17 are the sources of information and the sources of  
18 information would then set up discussion topic  
19 two, which is what's the role of labeling and  
20 informing your use of pharmacogenomic data in your  
21 practice?

22 And we are specifically interested, for

1       example, on where you might locate that in the  
2       label. Boxed warning, contradiction, warning and  
3       precautions, dosage administration -- our  
4       suspicion is that where you might put it might  
5       depend upon what the nature is of those data and  
6       what are the clinical implications of using that  
7       information and we specifically then prompt you  
8       with two of the examples that we have put on the  
9       table. One would be the POLG test prior to  
10      prescribing valproic acid and the other would be a  
11      CYP2D6 test prior to prescribing atomoxetine and  
12      how would you see the use of those pharmacogenomic  
13      data in your use of that and then finally, we are  
14      interested in how you described that to your  
15      patients to some extent helping to understand  
16      what's the role of labeling and informing that  
17      practice?

18                   So the idea is to have a hopefully  
19      stimulating and useful discussion of the role of  
20      pharmacogenomic data and with that, I guess I'll  
21      invite Dionna to come up and start us on this  
22      journey for the afternoon.

1 DR. GREEN: Thank you. So good  
2 afternoon. During my presentation, I will be  
3 providing you with a brief overview of the science  
4 of pharmacogenomics. I'll then describe the  
5 regulatory framework that supports this phase from  
6 a drug development perspective and I'll end by  
7 discussing the incorporation of pharmacogenomic  
8 information into FDA approved drug labeling and  
9 provide some considerations as to this application  
10 to the care of pediatric patients. So ICH E15  
11 defines pharmacogenomics as the study of  
12 variations of DNA and RNA characteristics as  
13 related to drug response, or in other words, it is  
14 study of how an individual genetic makeup  
8 15 influences his or her response to a drug.

16 Patient response to drug therapy is  
17 highly variable and so for example, the effects of  
18 a certain dose of a drug may differ widely between  
19 individual patients where one patient may exhibit  
20 an effect while another may show no effect at all  
21 or only a partial effect.

22 In the same way, some patients may have

1 significant adverse effects while others do not.  
2 Genetic variation can influence drug disposition  
3 in drug pharmacokinetics in terms of how the drug  
4 is absorbed, distributed, metabolized and  
5 eliminated from the body as well as how the drug  
6 is transported in the body.

7           Genetic variation may also cause  
8 differences in intended target, or unintended  
9 target effects and ultimately can affect drug  
10 efficacy and safety. Now there are multiple  
11 covariates or variables that contribute to and  
12 help explain variability and drug response, things  
13 such as age, body size, and concomitant medications  
14 are all examples of covariates so genetics simply  
15 represents another covariate and as such, the  
16 inclusion of pharmacogenomic or genetic  
17 information in labeling provides an additional  
18 means for prescribers to tailor drug therapy to  
19 the individual patient.

20           So when assessing drug response, of  
21 course, we know that clinical outcomes provide a  
22 direct measure of how a patient feels, functions

1 or survives in response to a therapeutic  
2 intervention.

3 On the other hand, a biomarker is a  
4 defined characteristic that is measured as an  
5 indicator of a normal process, a pathogenic  
6 process or as an indicator of response to a  
7 therapeutic intervention.

8 Molecular, histological, radiographic or  
9 physiologic characteristics all represent types of  
10 biomarkers, as does DNA or RNA characteristics,  
11 which are considered genomic biomarkers. More  
12 specifically, biomarkers can be characterized  
13 based on their functionality so there are  
14 diagnostic biomarkers, ones that are for  
15 monitoring for pharmacodynamic and response  
16 biomarkers, there are also predictive and  
17 prognostic biomarkers as well as safety and  
18 susceptibility biomarkers and so for more on this,  
19 I would please refer you to the best resource,  
20 which is the biomarkers, endpoints and other tools  
21 resourced which is a living glossary brought forth  
22 by an FDA/NIH collaborative effort and it

1 essentially provides harmonized definitions on  
2 categories of biomarkers and endpoints and further  
3 describes their role in clinical practice,  
4 clinical research and drug development.  
5 Biomarkers play an essential role in precision  
6 medicine. When the term precision medicine is  
7 used, it is generally referring to a drug product  
8 that is intended for use with a genomic, proteomic  
9 or other specific biomarker and in this context,  
10 the biomarker can be used to identify patients  
11 within a disease who are eligible for treatment  
12 with that drug.

13           It can aid in determining the  
14 appropriate dose or it can allow for monitoring  
15 drug response in order to individualize therapy.  
16 As I mentioned, biomarkers can have diagnostic  
17 value, predictive value or other value and in most  
18 cases, there is an underlying assumption that  
19 there is a mechanistic relationship between the  
20 biomarker and the drug of interest.

21           So there are various strategies for  
22 incorporating biomarkers and specifically in the

1 cases for today's presentation, genomic biomarkers  
2 and clinical drug development. In the early  
3 exploratory phase, for example, one approach may  
4 involve taking all comers into a trial where you  
5 may be looking to explore or identify novel  
6 biomarkers that may help in predicting patient  
7 response and again, this could be a biomarker that  
8 has several functional components, including one  
9 that's for prognosis, prediction, diagnosis and so  
10 on.

11 Another approach may be that you already  
12 know something about a particular biomarker and  
13 you want to use that information to streamline the  
14 trial and attempt to achieve early proof of  
15 concept based on that biomarker. At later phase  
16 trials, when you are confirming clinical benefit,  
17 you can use the genomic biomarker, for example, or  
18 any biomarker and all the information that you've  
19 gathered to either enrich your study population or  
20 to stratify randomization in order to test various  
21 hypotheses.

22 Ultimately, the goal here would be for

1       this data that's been gathered to be translated into  
2       informing clinical decision making and perhaps with  
3       the use of some test and clinical practice that  
4       would help the provider prescriber to pick an  
5       appropriate dose, select which patients to receive  
6       that drug or allow for patient monitoring.

7                 So there is a vast utility for a genomic  
8       data and drug development. It includes being able  
9       to service the basis for investigating  
10      pharmacokinetic and pharmacodynamic outliers or  
11      for explaining intersubject variability as  
12      previously mentioned.

13                A genomic biomarker, for example, could  
14      also be used to prospectively enrich the study  
15      population or in a trial of all comers, it could  
16      be used in the analysis for subgroups. It can also  
17      be used to estimate the magnitude of a potential  
18      drug-drug interaction and importantly, it can  
19      provide great utility for investigating the  
20      molecular or mechanistic basis for a patient's  
21      lack of efficacy or the presence of an adverse  
22      drug effect.



1                   So now I want to describe the regulatory  
2                   framework that supports pharmacogenomics. Since  
3                   the early 2000s, FDA has committed efforts and  
4                   resources towards a myriad of genomic related  
5                   initiatives and activities, some of which include  
6                   hosting various public workshops on a wide variety  
7                   of topics, developing guidance on topics such as  
8                   pharmacogenomic data submission, collection of DNA  
9                   in clinical trials and later on topics such as  
10                  companion diagnostics and trial enrichment.

11                  Other activities have included the  
12                  launch of the biomarker qualification program as  
13                  well as the integration of genomics into  
14                  regulatory drug review. And most recently,  
15                  clarifying the process for drug diagnostic code  
16                  approvals of which we are seeing more and more of.  
17                  So over the years, FDA has gathered its  
18                  experiences and translated them into what has  
19                  hopefully been received as pragmatic and relevant  
20                  guidance for industry.

21                  As I previously mentioned, there have  
22                  been a number of documents published which have

1 outlined the regulatory framework for the  
2 incorporation of pharmacogenomics and target  
3 approaches into drug development as well as into  
4 drug labeling and many are listed here.

5 I will not go through each one but for  
6 the purposes of today's talk, I will briefly  
7 highlight a few principles from two FDA guidances.

8 The first is the clinical  
9 pharmacogenomics guidance and it deals with early  
10 phase studies and the collection of DNA. An  
11 important prerequisite to successful use of  
12 genetic information in drug development is the  
13 collection of DNA from a large number of trial  
14 participants. So in those cases when there are  
15 known genetic factors or genomic factors that are  
16 likely to influence drug efficacy, safety or  
17 dosing, then collection of DNA from all subjects  
18 in a trial is recommended. When there is high  
19 variability in drug concentrations or in responses  
20 or there are ethnic differences or serious  
21 toxicities observed, it's recommended that DNA be  
22 collected from as many subjects as possible and

1 that data to be used in the future for exploratory  
2 studies.

3           The next guidance I want to touch upon  
4 is the one that addresses enrichment strategies  
5 for clinical trials. Enrichment is defined as the  
6 perspective use of any patient characteristic to  
7 select the study population in which detection of  
8 a drug effect, if there is in fact one, is more  
9 likely than it would be in an unselected  
10 population.

11           And so patients with the marker of  
12 interest would be considered marker positive. A  
13 genomic marker can be an example of a patient  
14 characteristic that can be used to enrich a study  
15 population and this draft guidance addresses  
16 considerations when targeting specific subgroups  
17 of patients including molecularly defined  
18 populations. Enrichment strategies can be used for  
19 three broad categories, including simply  
20 decreasing the noise of a trial or, for prognostic  
21 reasons, such as choosing patients who are more  
22 likely to have a disease related condition in the trial

or

1 for predictive reasons in terms of selecting those  
2 patients who are more likely to respond to the  
3 drug.

4           The guidance also provides  
5 considerations for marker negative patients, such  
6 as when to study them and the types and amount of  
7 data needed in those groups. So now I want to  
8 switch gears for the remainder of the presentation  
9 to talk about the incorporation of pharmacogenomic  
10 information in drug labeling. So in general, the  
11 purpose for the inclusion of pharmacogenomic  
12 biomarker based information and labeling is to  
13 primarily inform the prescriber about the impact  
14 of genotype on phenotype and to indicate whether a  
15 genetic test is available. In cases where a  
16 genetic test is available, labeling should  
17 communicate whether testing should be considered,  
18 is recommended or is necessary.

19           Some drug labels do include a specific  
20 subsection focused on pharmacogenomics but in  
21 general, it's important to note that genomic or  
22 genetic information may be located in various

1 places throughout the drug label. The types of  
2 genomic information may include information on  
3 allele frequencies, the description of the  
4 functional effects of genomic variance, the effect  
5 of genotype on pharmacokinetics and  
6 pharmacodynamics and dosing and/or patient  
7 selection strategies based on genotypes. There  
8 are now upwards of 160 drug labels containing  
9 pharmacogenomic information with over 50  
10 biomarkers described in those labels, the majority  
11 of which are related to drug metabolism or drug  
12 transport. About a third are related to the drug  
13 target or the disease pathway and about a quarter  
14 are associated with immunologic response or other  
15 safety considerations.

16           Pharmacogenomic information and labeling  
17 ranges from being purely for informational  
18 purposes so no action involved to being  
19 actionable, including considerations or  
20 recommendations for genetic testing as well as  
21 recommendations for perspective dosage adjustments  
22 and patient selection. At this point, roughly

1                   50 percent of the pharmacogenomic  
2 information contained in labeling is considered  
3 actionable. It's important to keep in mind the  
4 developmental aspects of pharmacogenomics.  
5 Developmental pharmacogenomics represents the  
6 dynamic change in gene expression that accompanies  
7 the maturation process which extends from  
8 embryonic life through adolescence.

9                   Interpretation of these changes is  
10 confounded by the inherent variability that exists  
11 in PK and PD as children grow, coupled with the at  
12 times limited understanding of the genetic basis  
13 for certain pediatric diseases.

14                  All of this makes accurate predictions  
15 of the effect of complex interactions of  
16 polymorphic enzymes, transporters and receptors on  
17 pediatric drug response at times challenging and  
18 is the basis for why genotype/phenotype  
19 relationships in adults may not always be  
20 reflective of those in children which leads me to  
21 the publication that I am going to discuss for the  
22 remaining of the presentation.

1                   This paper was published in the June  
2                   2016 issue of CPT, the Clinical Pharmacology and  
3                   Therapeutics journal. It was part of the  
4                   background materials for this meeting. It  
5                   discusses pharmacogenomic information and drug  
6                   labeling in its application to pediatric patients.

7                   This was a systematic survey of FDA  
8                   approved drug labels of which the objectives were  
9                   to identify those labels that have incorporated  
10                  pharmacogenomic data to determine the source of  
11                  the pharmacogenomic data as being derived from  
12                  either adult or pediatric studies and to assess  
13                  the suitability of applying adult derived  
14                  pharmacogenomic related findings and  
15                  recommendations directly to the care of  
16                  pediatrics.

17                  So the drugs at FDA database, the DailyMed  
18                  website and the FDA table of pharmacogenomic  
19                  biomarkers were searched for drug labels approved  
20                  between 1945 and 2014. This search was then  
21                  narrowed to only include those drug labels for  
22                  drugs which had been evaluated in pediatric PK,

1 safety and/or advocacy studies.

2 Genomic biomarkers described in labeling  
3 were categorized as being related to drug safety  
4 and/or efficacy and for the purposes of this  
5 analysis as being either associated with drug  
6 metabolism or transport, as influencing  
7 susceptibility to disease progression or adverse  
8 effects as predisposing to toxicities such as  
9 immune reactions or as being associated with the  
10 pathophysiology of the disease or the intended  
11 or unintended targets of the drug. Any  
12 pharmacogenomic related prescribing statements  
13 that were captured in labeling were recorded as  
14 part of this analysis.

15 And so the search identified a total of  
16 65 drugs that had been evaluated in pediatric, PK,  
17 safety and/or efficacy studies and whose drug  
18 labels also happened to contain pharmacogenomic  
19 data. The most common therapeutic areas that were  
20 represented included psychiatry, oncology and GI.  
21 There were 31 different biomarkers, different  
22 genomic biomarkers described in these labels, the



1 majority of which were related to drug metabolism  
2 and transport.

3           Almost 70 percent of the 31 biomarkers  
4 had an association with drug toxicity while the  
5 remaining had consequences related to drug  
6 efficacy. 28 of the 65 drug labels included a  
7 prescribing statement based on a genomic biomarker  
8 and those statements ranged from  
9 contraindications, warnings, dosage adjustments,  
10 patient selection information or noting the  
11 availability or recommending genetic testing.

12           For 86 percent of the drugs, the genetic  
13 biomarker data described in labeling was derived  
14 from adult studies. Of the nine cases where  
15 labeling was informed directly by data obtained in  
16 pediatric studies, the majority involved diseases  
17 that originate primarily or occur only in  
18 childhood. For the 56 drug labels with adult  
19 derived data, the application of that data to  
20 pediatrics was deemed suitable for about 70  
21 percent of the drugs and unclear for the remaining  
22 30 percent.

1           Of those that were deemed unclear, 11  
2 cases involved pediatric studies that enrolled  
3 children less than two years of age in either a  
4 clear, conflicting or unknown effect of ontogeny  
5 on the genetic biomarker.

6           The remaining five cases involved a  
7 target or a pathway related genomic marker that  
8 was specific to the adult disease which differed  
9 substantially from the pediatric disease studied.

10           So in summary, pharmacogenomic  
11 information is increasingly being incorporated  
12 into drug labeling and this information can aid  
13 prescriber in tailoring drug therapy for the  
14 individual patient. The majority of  
15 pharmacogenomic information in drug labeling is  
16 derived from adult studies.

17           Developmental differences in gene  
18 expression, drug response and drug metabolizing  
19 capacity, for example, can all result in an  
20 inability to universally assume similar genotype,  
21 phenotype relationships between adults and all  
22 pediatric age groups.

1                   The application of adult derived  
2           pharmacogenomic information to pediatrics is  
3           particularly challenging when attempting to apply  
4           those findings and recommendations to the youngest  
5           pediatric patients. So for example, neonates and  
6           infants, or when there are substantial differences  
7           between the adult and pediatric disease, thank  
8           you.

9                   DR. HUDAK: Okay, unless there are any  
10           particular questions now, we'll go on to the next  
11           presentation. So Michael Pacanowski, if you can  
12           say a couple of words of background about  
13           yourself, that'd be great.

14                   DR. PACANOWSKI: Good afternoon,  
15           everyone. My name is Mike Pacanowski, I am the  
16           associate director for genomics and target therapy  
17           in CDER's Office of Clinical Pharmacology. I've  
18           been with the FDA for several years. I am a  
19           clinical pharmacologist by training. My main  
20           interest is in genetic epidemiology and  
21           pharmacogenetics.

22                   So what we decided to do is to go

1 through a couple of different case studies to give  
2 a more deeper understanding of some of the issues  
3 that were considered as part of the labeling  
4 process for certain pharmacogenetic interactions.  
5 Trying to contrast a couple of issues, some  
6 related to the safety of the products, some  
7 related to the drug's disposition. What we did not  
8 pick are the myriad examples of drugs where we  
9 have a disease that's defined by genetic  
10 characteristics and being targeted as such with  
11 specific mechanisms of action as would be the case  
12 for Duchenne muscular dystrophy or cystic fibrosis or  
many of the  
13 other disease that are genetic in nature.

14           So the cases we've chosen really serve  
15 to highlight different points in the process.  
16 Following the cases, I'll discuss a couple of the  
17 review considerations related to the evidence and  
18 some of the thought processes behind how some of  
19 our recommendations translate into labeling with  
20 regards to how the drug is used or whether a test  
21 should be ordered so the examples are listed out  
22 here. Just pointing out, for the first three

1 examples, the issue that we are mainly concerned  
2 with is safety and in two of the cases it's  
3 related to the drug metabolism. In the first case,  
4 the data generally emerged in the post-market  
5 setting whereas for atomoxetine a lot of those  
6 data were able to be collected in the premarket  
7 settings as was evidenced in the original labeling  
8 for the product. For valproic acid, this was a  
9 post-marketing safety issue that was reviewed by  
10 our offices on renal epidemiology as well as new  
11 drugs in clinical pharmacology and then  
12 clopidogrel, which I'll note does not have an  
13 indication for use in children was another issue  
14 that occurred in the post-market setting and is  
15 related mainly to the efficacy of the product.

16           So I won't belabor this case too much  
17 because this was something that was discussed  
18 extensively to the prior advisory committee but  
19 we'll just touch on it to close the loop and  
20 update you as to what's been changed in the  
21 labeling since the pediatric advisory committee  
22 last year. So as you know, efavirenz is an

1 antiretroviral drug. It's used in combination with  
2 antiretroviral agents for HIV 1 infections. It is  
3 indicated for use in children who are at least  
4 three months of age and weigh at least three and a  
5 half kilograms.

6 It's an NRTI, non-nucleoside reverse  
7 transcriptase inhibitor, and it has a number of  
8 side effects associated with it, the most  
9 prominent among them being hypersensitivity  
10 reactions, drug interactions, QT prolongation as  
11 well as neuropsychiatric events, hepatotoxicity  
12 and rash. So the metabolism of the efavirenz is  
13 mainly through cytochrome CYP3A as well as CYP2B6,  
14 so those are the two main cytochromes involved and  
15 it's elimination from the body.

16 There is evidence that with continued  
17 dosing of the drug, that there is autoinduction so  
18 it's able to induce it's own metabolism which can  
19 obviously complicate some of the pharmacokinetic  
20 interactions that could be seen.

21 CYP3A is generally not regarded as being  
22 polymorphic so there is not a lot of genetic

1 variations that influence the disposition of drugs  
2 metabolized by CYP3A. There are some rare  
3 variations in CYP3A4, CYP3A5, the sister enzyme is  
4 highly polymorphic but with the abundance of the  
5 enzyme, it generally does not have a very profound  
6 impact on substrates of this enzyme.

7 CYP2B6, on the other hand, does have  
8 some common reduced or loss of function alleles,  
9 including the \*(star)6 allele and \*(star)18 allele and  
10 it's estimated that roughly 6-12 percent of white  
11 populations, 14-38 percent of black and African  
12 American populations and 1-4 percent of Asian  
13 populations are poor metabolizers, meaning they  
14 have two reduced function alleles and  
15 consequently -- have a lower capacity to  
16 metabolize substrates of this enzyme. For  
17 efavirenz specifically, relative to normal  
18 metabolizers, CYP2B6 for metabolism has resulted  
19 in effects of the pharmacokinetic of efavirenz.  
20 We've seen higher drug concentrations, about  
21 two-fold higher, total exposures. There has also  
22 been many published reports of higher rates of

1 virologic suppression and immunologic response to  
2 the drug, beneficial effects that are related to  
3 having potentially the higher exposures in this  
4 population but we've also seen marginally higher  
5 rates of hepatic and central nervous system side  
6 effects with this medication.

7           So this is all based on published  
8 literature, there have been a number of studies  
9 but I think you can gather from this that there is  
10 really no clear evidence one way or the other as  
11 to whether a dosage strategy based on genotype  
12 would have positive outcomes in the clinical  
13 setting. So essentially there is some uncertainty  
14 about whether reducing a dose for a given genotype  
15 might offset the efficacy issues. Conversely,  
16 going higher on the dose in certain patients might  
17 also result in some toxicity.

18           The other issue is with some of the  
19 central nervous system, toxicities tend to resolve  
20 with time if patients are able to persist with  
21 therapy which also potentially argues against a  
22 genotype based dosage strategy.



1           There is a balance between maintaining  
2           this risk benefit balance. There is also a little  
3           barrier to resistance and with all of that said,  
4           there has not been any clear recommendation in FDA  
5           labeling with regard to the need for genotyping  
6           for this product.

7           I'll also note, as was mentioned before  
8           that the guidelines do recommend that children who  
9           are three years and above have a weight based  
10          dosing regimen whereas those who are under three  
11          years of age who absolutely require treatment,  
12          that they undergo genotyping to have an  
13          investigational dosing used in that population so  
14          the guidelines have covered that issue.

15          In the past couple of months, there were  
16          data submitted to FDA to support a labeling  
17          revision, mainly the basis of a QT study that was  
18          performed so there is some 2B6 genotype  
19          information that has been included in labeling  
20          mainly to describe the differences in  
21          pharmacokinetics and differences in the extensive  
22          QT prolongation that was observed in this healthy

1 subject study so that was in August of 2016.

2           Moving on to the next example, valproic  
3 acid is a drug that's been around obviously for  
4 many years. It's indicated for seizure disorders  
5 as well as some psychiatric indications. The  
6 mechanism of this drug is not well established but  
7 it may be related to increases in bringing  
8 concentrations of GABA and has a rather long list  
9 of warnings around its use. I think many of you  
10 are probably familiar with this medication.

11           One of the most important, perhaps, is  
12 the hepatotoxic effects of this medication. There  
13 have been a number of cases of severe  
14 life-threatening hepatotoxicity that has been  
15 observed and it is estimated to be about 1 in  
16 10,000 incidence in the general population but as  
17 you get into younger age groups, the incidence  
18 clearly, increases quite strikingly, 1 in 500 in  
19 children under two years of age. It's a very  
20 significant adverse effect of this medication.

21           So over the years, there has been a  
22 syndrome that has been characterized, basically

1 related to mitochondrial disorders. Polymerase  
2 gamma is an enzyme that replicates mitochondrial  
3 DNA. There are mutations that are present in this  
4 but it causes a really wide spectrum of clinical  
5 presentations and it can range anywhere from fatal  
6 encephalopathy in very young children to much more  
7 subtle disorders in older adults such as migraine.

8           In very young children, it frequently  
9 manifests as treatment refractory epilepsy and is  
10 sometimes associated in and of itself with hepatic  
11 dysfunction. So FDA, a couple of years ago,  
12 reviewed a number of published literature reports  
13 as well as reports that were submitted through  
14 fairs for valproic induced liver failure as well  
15 as looking at the natural history of POLG  
16 disorders and other mitochondrial disorders where  
17 you might ostensibly think that valproic could  
18 have an issue.

19           What we identified basically from the  
20 published literature was that valproic acid  
21 resulted in liver failure in roughly 61 out of 65  
22 patients who had a POLG related disorder. In many

1 cases, the presence of the POLG disorder was  
2 defined by valproic induced hepatic failure,  
3 however, in the absence of valproic acid, about  
4 20-40 percent also developed some type of hepatic  
5 dysfunction.

6 In addition, valproic acid results in  
7 hepatotoxicity only in about 3 of 26 patients who  
8 had other mitochondrial disorders such as MELAS  
9 and MERRF and a lot of these other mitochondrial  
10 problems.

11 Looking at POLG more closely, there are  
12 over 200 mutations that have been reported. Among  
13 those patients who had valproic induced liver  
14 failure, about two thirds of the cases had at  
15 least one copy of these two specific mutations so  
16 a screening strategy that would focus on these  
17 might capture a large proportion of the patients,  
18 who might be at risk. Carriage of POLG mutations  
19 is also, outside of this setting, exceedingly rare  
20 so it's not something that could be done in a  
21 broader population setting.

22 So we basically have evidence derived

1 from published and reported case reports or case  
2 series that didn't really have very systematic  
3 capture, various exposures of even the hepatic  
4 pathology that patients were presenting with but  
5 we do know that many of the patients did go on to  
6 have a fatal outcome. The POLG mutations  
7 themselves result in a really wide spectrum of  
8 disorders that are really a variable (inaudible)  
9 and very age dependent so it becomes hard to start  
10 basing a screening strategy on clinical features  
11 alone because it can be so broad. And we also  
12 know that as time goes on, into adulthood, the  
13 risk of valproic induced liver failure decreases  
14 substantially. That being said, there are some  
15 signals that do point to certain patients who  
16 might be clinically suspected of having  
17 mitochondrial disease and as such, in labeling, we  
18 target recommendations to focus on those  
19 particular features and advising that screening  
20 would be best suited for those patient  
21 populations.

22 Now we also understand that this isn't

1 going to capture all patients but it's sort of a  
2 first step to screen patients to rule out a  
3 potential for a very serious outcome. There are  
4 also, in POLG, a number of other more common  
5 mutations that have much more conflicting  
6 literature around them and we are really unclear  
7 on the predictive utility of how testing for those  
8 might help reduce the risk of this serious  
9 outcome.

10           So the labeling was revised. There is a  
11 boxed warning related to the hepatotoxicity and  
12 that patients who are basically under the age of  
13 two or who have a mitochondrial disorder should  
14 not be receiving this medication. It is contraindicated  
15 in patients who have a known  
16 mitochondrial disorder caused by a POLG mutation  
17 and otherwise suspected of having POLG related  
18 disorders under two years of age.

19           The warnings provide a fair amount of  
20 information related to what was reported, the  
21 characteristics of how these patients might  
22 present and makes -- provides some advice on

1 screening and clinical practice, noting the two  
2 most common alleles that might be captured but  
3 nonetheless, patients should be monitored very  
4 carefully for liver abnormalities when receiving  
5 this medication. So that wraps up the  
6 POLG/valproic acid interaction. We'll move on to  
7 another drug metabolism example. So this is  
8 atomoxetine. It's indicated for the treatment of  
9 the treatment of attention deficit and  
10 hyperactivity disorder. It's a selective  
11 norepinephrine reuptake inhibitor and has a number  
12 of warnings that are listed out here as well.

13           Among them, cardiovascular and  
14 hemodynamic effects, psychosis, behavioral issues  
15 as well as drug interactions are included in the  
16 warnings statements for this product. So CYP2D6  
17 is actually a relatively clean substrate for --  
18 atomoxetine is a relatively clean substrate for  
19 CYP2D6.

20           CYP2D6 is pretty well characterized --  
21 it's a very complex gene from a drug metabolism  
22 standpoint. It has a number of genetic variations

1 that influence its function and ability to  
2 metabolize substrates of the enzyme but bottom  
3 line, it's roughly 5-10 percent of white  
4 populations, 2-5 percent of black or African  
5 American populations and under 1 percent of Asian  
6 populations are regarded as poor metabolizers,  
7 meaning they have reduced ability to clear  
8 substrates of the enzyme. For atomoxetine, the  
9 effects on the drug are very clear across the  
10 different subgroups based on CYP2D6 metabolic  
11 status. Here we see roughly tenfold variation and  
12 concentrations fivefold higher maximal  
13 concentrations and a significantly prolonged  
14 half-life of the product.

15           Additionally, in labeling the -- all the  
16 adverse events that were observed in the  
17 pre-market program are listed out very clearly  
18 based on metabolic status and you can see those  
19 for insomnia, weight loss and so on here so there  
20 is a clear difference in adverse event rates.

21           So in this setting, we had evidence from  
22 premarket clinical trials and a fairly reasonable



1 understanding of how the enzyme affected the drug  
2 concentrations in this case. There are multiple  
3 strengths of the drug product available and it is  
4 a go slow type of medication so it is titrated to  
5 an effect but the labeling does recommend that  
6 escalation from the lowest starting dose in known  
7 PMS, really depends on the persistence of the  
8 symptoms as well as it's tolerability profile so  
9 it is more individualized in that regard.

10 The prescribing recommendations in here  
11 are very analogous for the CYP2D6 drug  
12 interactions and the PK in safety findings are  
13 stratified in labeling by metabolic status  
14 throughout. So I won't go into all the details of  
15 the labeling but suffice to say that number of the  
16 sections of the labeling contain this information.

17 There are explicit dosing instructions,  
18 a clear depiction of the adverse event rates and  
19 the warning specifically with respect to  
20 hemodynamic effects and all of the PK particulars  
21 are detailed in the clinical pharmacology section.

22 The last example I'll walk through is

1 for clopidogrel and CYP2C19. This is a drug that's  
2 currently indicated for acute coronary syndromes,  
3 recent MI, recent stroke and established  
4 peripheral artery disease in adults. It is a P2Y12  
5 inhibitor of platelet aggregation and the major  
6 warnings that this drug currently has related to  
7 the impaired CYP2C19 function as the antiplatelet  
8 medication.

9           Obviously bleeding is a warning for it  
10 as well as some other reactions that have been  
11 observed. So clopidogrel is unique in that it's a  
12 prodrug, it's activated by a number of different  
13 enzymes in the body, relatively small proportion  
14 of the parent compound is actually converted to an  
15 active metabolite that inhibits the platelets but  
16 esterases basically clear most of the parent  
17 compound. CYP2C19 has been identified as a critical  
18 factor in the activation of this drug and this is  
19 an enzyme that we know has reduced function in a  
20 number of different populations and it does tend  
21 to be more common in Asian, Southeast Asian  
22 populations.

1                   So relative to normal metabolizers,  
2           CYP2C19 metabolizers tend to have lower active  
3           metabolite concentrations, they tend to have  
4           diminished antiplatelet effects and there have  
5           been a number of retrospective studies that have  
6           shown higher rates of cardiovascular events,  
7           perhaps amongst the most concerning being higher  
8           rates of stent thrombosis in adults among poor  
9           metabolizers relative to normal metabolizers.

10                   So in this case we had really a mix of  
11           evidence that was collected from the published  
12           literature using retrospective analyses of  
13           clinical trials but we also had the sponsor  
14           conduct some pharmacokinetic studies to help  
15           further characterize the drug interaction or the  
16           drug gene interaction.

17                   We did have a fair amount of outcome  
18           studies. In some cases, this was conflicting  
19           depending on what they might have tested or what  
20           types of outcomes they were measuring. Really  
21           having a good sense of this interaction. Premarket  
22           was a little bit difficult because the active

1 metabolite is very transient and very difficult to  
2 characterize and when we look at sort of more  
3 broadly, the spectrum of pharmacodynamic measures,  
4 there is a lot of variability in how those are  
5 conducted, they are very technical and basically  
6 what we observed was a rather consistent effect  
7 across multiple different models of antiplatelet  
8 effects. There was some evidence that altered  
9 dosing doesn't really appear to really compensate  
10 for this reduced metabolite exposure but there  
11 were alternative treatment options that had become  
12 available following its approval.

13           Additionally, with regard to genetic  
14 testing, the treatment context is often acute so  
15 you need a test that can turn around relatively  
16 quickly but there are also different approaches to  
17 doing this in the acute setting where you could  
18 start one drug or another and then await the test  
19 result and change the course of therapy after  
20 that.

21           So, this gene drug interaction is  
22 outlined in the boxed warning for the product as

1 well as in the warnings and precautions section and  
2 there is some detail of the studies that were  
3 conducted to further characterize it in the  
4 clinical pharmacology section.

5           So I'll spend the next couple of minutes  
6 just touching on some of the issues that we tend  
7 to tune into when looking for gene drug  
8 interactions and how to manage them. As was  
9 mentioned in the previous talks, the types of  
10 things that we tend to look for are very high  
11 degrees of concentration or response variability.  
12 We look for things that are very obvious, like a  
13 multimodal distribution in the pharmacokinetic  
14 profile where you see a cluster of individuals  
15 that might have very high exposure. We also look  
16 for race effects, geographic effects on exposures  
17 or responses that might suggest there might be  
18 some genetic underpinnings as well as outlining  
19 concentrations are generally subject to further  
20 investigation using genetic analyses to help  
21 characterize and understand why they occur.

22           So from a pharmacokinetic and response

1 perspective, those are the things that we tend to  
2 look for. Obviously, if it's a substrate for a  
3 polymorphic enzyme or transporter, we'll have  
4 sponsors look at those issues very carefully to help  
5 characterize the potential for an interaction and  
6 in other cases, if there are severe toxicities or  
7 adverse events, we'll have those investigated more  
8 closely so there is a number of factors that would  
9 signal the need for further genetic studies.

10           Looking at the labeling in sort of the  
11 high-level overview. A lot of the data that we end  
12 up having to react to emerge in a post-market  
13 setting and it's really often external to the  
14 sponsor's clinical trials. The adverse events that  
15 we've taken action on in the post-market setting  
16 have typically been pretty severe and very well  
17 replicated so very clear that there is well  
18 established interaction between the gene and the  
19 drug and some outcome.

20           Many of these -- the story is a little  
21 bit easier. We have some pharmacokinetic basis for  
22 example to make the dosing recommendations or the

1 testing recommendations because it's analogous to  
2 how we handle drug interactions that we really  
3 never have these well-designed prospective  
4 validation studies so it really has to -- we  
5 really end up having to triangulate multiple lines  
6 of evidence, number one, to understand if the  
7 interaction is valid and then also what to do with  
8 it.

9           So some of the considerations, as  
10 mentioned, we have, in some cases, sponsor  
11 conducted trials which are reasonably well  
12 controlled and in other cases, published  
13 literature which we have to end up viewing in  
14 aggregate and in some cases we can't do controlled  
15 studies such as for a very adverse event,  
16 obviously, so we end up, for severe toxicities and  
17 looking at outliers, more of the case report or  
18 retrospective case control types of analyses, for  
19 efficacy, safety and PK outcomes, we have either  
20 prospective or retrospective cohort studies or  
21 actual genotype guided control trials that  
22 specifically evaluate that hypothesis.

1                   So with such a spectrum of evidence,  
2                   causal inference in this space is really informed  
3                   by mechanistic information, consistency across  
4                   studies, the presence of dose response and really  
5                   the magnitude of interaction and statistical  
6                   significance so your typical Bradford Hill  
7                   criteria.

8                   That then -- whether it's real or  
9                   potentially real interaction, that becomes the  
10                  subject of review and then how to handle that in  
11                  terms of a labeling then becomes the question so  
12                  we are clearly left with many questions often in  
13                  these cases dealing with retrospective evidence or  
14                  published studies, specifically whether genotyping  
15                  strategies effectively reduce the risk of an adverse  
16                  event, the quality of the studies may be a  
17                  question mark in the published literature, there  
18                  may be gaps in empirical evidence so sometimes we  
19                  make inferences from a pharmacokinetic effect and  
20                  parlay that into what the potential likelihood of  
21                  a difference and the risk of adverse events would  
22                  be so there may be gaps in empirical evidence



1 where we don't have direct data in genotype  
2 subgroups about inefficacy or safety of a product.

3           The generalizability to diverse racial  
4 and ethnic populations is also an issue in the  
5 space of genetics because clearly the frequencies  
6 of some of these things do differ around the globe  
7 so we do take into consideration how severe the  
8 outcome is, what the treatment context is,  
9 specifically whether there are other therapies  
10 that could potentially be used, what types of  
11 monitoring tools are already in place to help  
12 manage risks as well as in the case of dosing,  
13 whether there are dosage forms that would even  
14 accommodate different accommodations. Test  
15 accessibility and feasibility is also an issue  
16 which Kellie will talk about more in the next  
17 presentation and prescriber uptake is clearly, at  
18 the moment, not something that's universal so we  
19 have to consider what the likelihood of uptake  
20 might be as well.

21           With regard to the testing  
22 recommendations, often we are silent on whether

1 patients must be tested. We typically will make  
2 reference to a known status or consider genotyping  
3 really to accommodate that clinical judgement in  
4 individual patient context as well as some of the  
5 uncertainties on how to specifically manage the  
6 interaction. It's really done in an effort to  
7 inform prescribers that an interaction is present.  
8 However, when it's in the indication statements or  
9 the contrary indications, it's somewhat implicit  
10 that genetic testing should be performed to manage  
11 the interaction.

12                   When we do test or recommend testing,  
13 there is a variety of different approaches that  
14 can be taken, you can test every one as is the  
15 case for abacavir which has an HLA peptide interaction  
or  
16 and eliglustat which has a CYP2D6 interaction. You could  
17 test really targeted high risk subsets which is  
18 the case for carbamazepine which is based on a  
19 racial/ethnic profile or valproic acid which  
20 depends on clinical presentation or test above a  
21 certain dose threshold as is the case for pimozide  
22 for tick disorders and tetrabenazine which is for

1       Huntington's disease so once patients achieve a certain  
2       dose, then they get tested to determine how to  
3       further proceed if additional higher doses are  
4       needed.

5                       With regard to other considerations, the  
6       specific alleles, we generally do not get into in  
7       labeling, largely left to the prescribing  
8       community and lab community and we don't really go  
9       into much detail on the prevalence of different  
10      factors so to summarize, in close up, really the  
11      goal is to identify gene drug interactions that  
12      would help inform prescribing and shift the  
13      benefit, obviously. I think some of the case  
14      examples have illustrated that you prospectively  
15      and very proactively characterize some of these  
16      interactions in a premarket setting at least when  
17      it's a common genetic factor and we are interested  
18      in some common outcome or some continuous measure  
19      that can be easily detected.

20                      Rare events are obviously much more  
21      complicated and that also have translation issues  
22      because you start talking about introducing tests

1 that by definition may not have the perfect  
2 predictive qualities that we might be interested  
3 in for a diagnostic test and prescribing  
4 recommendations, really try to balance some of  
5 these uncertainties with what's needed to inform  
6 the prescribing community and with that, I'll  
7 close. Any clarifying questions or are we waiting  
8 for discussion?

9 DR. HUDAK: We thank you. A lot of  
10 information very quickly.

11 DR. PACANOWSKI: Sorry.

12 DR. HUDAK: Anybody have any pressing  
13 questions at this time? DR. White?

14 DR. WHITE: Just help me out a second,  
15 this CYP2D6, as I recall, has a very high incidence  
16 in the Middle Eastern population? It was like 30  
17 to 40 percent when we met with the coding studies.

18 DR. PACANOWSKI: So there is -- CYP2D6  
19 has a number of different genetic characteristics.  
20 You can have multiple copies of the gene which  
21 tends to be -- that issue tends to be a little bit  
22 higher in some of the Middle Eastern populations

1 where you have multiple copies of the gene which  
2 results in very, very high metabolism if you are  
3 duplicating a gene that's functional.

4 DR. WHITE: Okay, thank you.

5 DR. PACANOWSKI: Okay, thank you.

6 DR. HUDAK: Thank you. So now we move to  
7 analytical and clinical validation of  
8 pharmacogenetic tests. Another fascinating topic  
9 by Kellie Kelm. Thank you.

10 DR. KELM: Good afternoon. I am Kellie  
11 Kelm and I am from the Center for Devices and  
12 Radiological Health. We review medical devices  
13 both premarket and post-market and I am from the  
14 Division of Chemistry and Toxicology Devices and  
15 we have a wide range of products here. I have been  
16 here in the fall to also present some other  
17 devices so I am going to talk to you a little bit  
18 about when companies come in with test systems for  
19 pharmacogenetic testing, the kind of information  
20 we review in those premarket submissions. And so  
21 the outline is I'll briefly talk about the  
22 analytical validation, the clinical validation and

1 then I'll close up with some considerations, both  
2 clinical and analytical and some of these will  
3 touch on things that Mike just discussed as well.

4           So in terms of a premarket review of  
5 in vitro diagnostic devices, the regulations for  
6 medical devices for premarket review states that  
7 we should -- our review should be driven by the  
8 intended use of the device and so that is what is  
9 the description of the devices or conditions that  
10 the device is used to diagnose, prevent, treat,  
11 mitigate, et cetera and if applicable, what is the  
12 patient population for which the devices are to be  
13 used and then once we have that information, we  
14 assess what is the risk of an IVD and what are the  
15 consequences of the false result. We have three  
16 risk categories, we have the class one, the low  
17 risk and those products usually go right on the  
18 market, we don't even review those.

19           Class two, these are where most of our  
20 products are, moderate risk and in that case they  
21 go -- they submit a 510K to us which requires us  
22 comparing themselves to a predicate or device

1 that's legally marketed and either cleared by us  
2 or had been out in the market in 1976 and lastly  
3 there are class three devices. These are the high  
4 risk, these tend to be more rare and you have to  
5 have a class three if you are novel intended use  
6 and this goes through our premarket approval  
7 process.

8           So I give an example here of an intended  
9 use for a pharmacogenetic test system that we  
10 cleared so this is a 510K, a moderate risk claim  
11 and this test was a prescription use claim so for  
12 use by healthcare professionals and prescribers  
13 and so you can see it's a qualitative genotyping  
14 asset which can be used as an aid to clinicians in  
15 determining the therapeutic strategy for the  
16 therapeutics that are metabolized by the CYP2C19  
17 gene product and in this case, they had  
18 specifically detected \*(star)two \*(star)three and  
19 seventeen so these tests only provide information,  
20 genotype information.

\*(star)

21           There is no information -- this test  
22 doesn't give out on dosing but some laboratories

1       may make their own interpretation or have that  
2       information in house so this leaves it up a lot  
3       for the doctors to make their own determination of  
4       what they do with the information from the test.

5                So it's -- it's also already been  
6       described but pharmacogenetics is different from  
7       what we call classic genetic tests. Many potential  
8       patients can be tested, the phenotype is not  
9       obvious, usually prior to treatment. We already  
10      discussed why population differences in alleles  
11      and frequencies and in terms of the test, rare  
12      allele combinations can be hard to validate  
13      because they are hard to find and obviously we've  
14      already been talking about test results can drive  
15      drug safety and effectiveness.

16               So in terms of test performance,  
17      analytical validity and clinical validity is what  
18      we review and overall analytical validity means  
19      does my test measure the analytes that I think it  
20      does? Does it measure those analytes correctly or  
21      reliably?

22               And clinical validity, does my test



1 result correlate with the expected clinical  
2 presentation and how reliably does it do that. So  
3 this is the information that companies, with these  
4 pharmacogenetic test systems, will submit to us so  
5 we look at the tests reproducibility. So will I get  
6 the same result in repeated tests over time? Will  
7 I get the same result as someone else testing the  
8 same sample? So this evaluates how well the test  
9 works but also preanalytical steps, analytical  
10 steps, all those parts of the test and so how we  
11 do that is the companies do repeated testing of a  
12 set of samples.

13           They test from sample extraction all the  
14 way through test result and that captures the  
15 entire testing process and the testing should  
16 include multiple operators, instruments, lots of  
17 the region or any other components of the test  
18 system and number of days.

19           And for distributed kit, testing the  
20 same samples at multiple sites. Once again, can we  
21 capture the variability of the test system in  
22 multiple laboratories?

1                   So accuracy, will I get the result that  
2                   are the same as truth? Truth, for genetic testing,  
3                   typically and historically has been by directional  
4                   sequencing results. The studies should include  
5                   samples with all possible genotypes, unless a  
6                   genotype is very rare and the studies should have  
7                   sufficient samples to determine accuracy with some  
8                   set of predefined confidence. We also ask that  
9                   there be a study to evaluate the amount of DNA  
10                  that should be input or RNA or whatever feature of  
11                  the test. What is a minimum and a maximum amount  
12                  of DNA that could be input for the test to still  
13                  provide an accurate result and obviously you  
14                  should test what you recommend on your package  
15                  insert.

16                  Should we be worried about potential  
17                  interferences? There are endogenous and exogenous  
18                  interferences that could interfere with genetic  
19                  tests and we've seen those sometimes and this  
20                  could depend on, for example, sample type, so when  
21                  you are using DNA from saliva, is there an impact  
22                  when you -- the person giving you the sample has

1 eaten or had something to drink, et cetera, that  
2 you may, for example, need to put a limitation on  
3 them not having sample collection until some  
4 defined period of time after collection -- after  
5 the activity, before collection, excuse me.

6 We have actually seen impacts of  
7 different DNA extraction methods on test and  
8 lastly, is there some concern that your intended  
9 use population could have some characteristic of  
10 their samples that might be something that you  
11 should validate, for example, a candidate for  
12 taking Plavix could have high cholesterol  
13 triglycerides and if you are using a whole blood  
14 sample, is your extraction kit actually pretty  
15 robust, having very high levels of cholesterol or  
16 triglycerides.

17 So examples of the information that can  
18 be given to support clinical validity of the test  
19 includes generally three buckets that I have here  
20 so most commonly what we get is information from  
21 peer reviewed published studies that demonstrate a  
22 relationship between the genetic test result and

1 the selected clinical presentation and I have an  
2 example here of cystic fibrosis and delta F508.  
3 Less common for pharmacogenetics would be the next  
4 two so either a prospective analysis of a  
5 retrospective study or prospectively performed  
6 study so most companies tend to cite literature  
7 that has already been performed for genetics, not  
8 necessarily the company's test. So as I said,  
9 here are some clinical considerations and some of  
10 these have been touched on by Mike but as we look  
11 at some of the clinical information that companies  
12 provide for us to support their intended use, some  
13 of the issues that we've noted are that often the  
14 genetic studies, have been performed in homogenous  
15 populations and there can be other various  
16 exogenic factors that are important in other races  
17 and ethnicities and I gave an example of the  
18 (inaudible) where use of a limited genetic panel  
19 could cause harm in some groups. We've seen  
20 difficulties in resolving -- when papers are given  
21 to us, whether there are different interpretations  
22 of the clinical validity of genetic variance so

1       which genotypes are PM (poor metabolizers) and for  
example, should

2       intermediate metabolizers be included?

3               We've seen that results of studies  
4       evaluating CYP450 status and clinical outcomes  
5       have had discrepant results, so how do we resolve  
6       that and lack of improvement in clinical  
7       presentation or outcome over a standard of care  
8       that does not incorporate genetic information has  
9       also been seen.

10              So some of the analytical considerations  
11       that we've experienced, for example, there are  
12       technical issues -- some of the test systems might  
13       not be as good with these CYP450 genes or the  
14       suited efficiencies that had been known to occur.  
15       Rare variants not detected by a test so rare  
16       variants could prevent primer binding and  
17       sometimes companies do not evaluate ones that are  
18       close by that could be potentially interfering in  
19       primer binding. You know, the concern that a star  
20       one call, for example, means wild type but that  
21       rare variance could occur especially if a test  
22       only detects a small number of variants and then

1 of course, there's the fact that some of these  
2 polymorphisms have or share the same variants,  
3 making sure that the tests are actually detecting  
4 the discriminating allele.

5 So some tests take two days from sample  
6 processing through test results and then obviously  
7 if you are doing this in an offsite lab, there is  
8 time for shipping to laboratory. The shortest  
9 test, pharmacogenetics test that FDA has cleared  
10 is one that is a clinical laboratory test that  
11 requires a one hour turnaround but most of the  
12 ones that we have take at least four hours and in  
13 some cases take two so obviously that short term  
14 turnaround that Mike talked about is difficult  
15 with the ones that FDA has reviewed.

16 We are starting to see the next  
17 generation sequencing but we also have seen some  
18 discrepant information here where we see different  
19 technology as in sequencers from different  
20 companies are giving different results especially  
21 outside of those consensus sequences.

22 We see that different laboratories have

1 different interpretations of pathogenic, likely  
2 pathogenic, benign variance et cetera and  
3 companies with gene panels from different  
4 laboratories include different variants so if we  
5 see a study using patients that have gotten --  
6 have gene panels done from different sites,  
7 sometimes we don't have the same information for  
8 those patients.

9           So in summary, the analytical validation  
10 of pharmacogenetic tests that FDA reviews is  
11 robust. We are looking for an assessment of  
12 accuracy, of the reproducibility, that they've  
13 assessed the proper DNA input and potential  
14 interferences. Clinical validity information that  
15 we review can come from any sources and as I said,  
16 most of the time, it's actually from peer reviewed  
17 literature, not from the company itself and there  
18 are analytical and clinical considerations to keep  
19 in mind that can cause difficulties invalidating  
20 from exogenic tests and so that's it. Thank you.

21           DR. HUDAK: Thank you, Kellie. Any  
22 questions about the presentation?

1 DR. KELM: Thank you.

2 DR. HUDAK: All right, we'll go to our  
3 last speaker, DR. Leeder who is actually front and  
4 center on the clinical arena scene and the good  
5 news, DR. Leeder, is that you've got more than a  
6 half an hour if you want.

7 DR. LEEDER: Which is perhaps a good  
8 thing because I often abuse my privilege. My full  
9 name is James Stephen Leeder, I go by Steve. I  
10 have been working in the area of pediatric  
11 clinical pharmacology now for almost 35 years. The  
12 first 14 years were at the Hospital for Sick  
13 Children in Toronto and the last 20 plus have been  
14 at Children's Mercy Hospital in Kansas City.

15 There, I serve as director of the  
16 Division of Clinical Pharmacology, Toxicology, and  
17 Therapeutic Innovation in the Department of  
18 Pediatrics and I have some other administrative  
19 responsibilities as associate chair for research  
20 for the Department of Pediatrics and Deputy  
21 Director of the research institute there. I have a  
22 lot of interest in pharmacogenetics as applied to



1 drug therapy in children and I'd like to thank my  
2 colleagues who have spoken before me for giving me  
3 a fair bit of license on how I am going to tackle  
4 this topic of clinical implementation.

5           So first, my disclosures: I try to avoid  
6 interactions with the pharmaceutical industry  
7 because it makes my annual reporting as a special  
8 government employee very difficult. The purpose of  
9 the waiver was this atomoxetine study that was  
10 supported by an R01 grant from the National  
11 Institute of Health. And in fact, some additional  
12 work that -- where we are taking that particular  
13 study now, is supported by that grant at the  
14 bottom of the slide. It's a U54 grant from NICHD  
15 and we are one of four specialized centers for  
16 research and pediatric and developmental  
17 pharmacology.

18           So what I am going to do in my 30  
19 minutes. I am going to try not to abuse the  
20 privilege is I am going to talk about three  
21 challenges that face clinical implementation of  
22 pharmacogenomic information in pediatric

1 populations and I am going to -- we are going to  
2 discuss a little bit the challenges of applying  
3 population data to individual children because at  
4 the end of the day, that's really what we are  
5 after, trying to predict drug response or what --  
6 try to anticipate what the consequences of  
7 introducing a small molecule with therapeutic  
8 intent into a biologically dynamic system such as  
9 a growing and developing child.

10 In many cases, pharmacogenetics or  
11 pharmacogenomics have focused on the primary  
12 polymorphic pathway of elimination so we are going  
13 to talk a little bit about some challenges in  
14 limiting our discussion of pharmacogenomics to  
15 just the primary pathway and one of my biggest  
16 bugaboos is trying to scale adult data to inform  
17 what might be going on in children. I acknowledge  
18 that it is important to use as much information as  
19 we have available to us to inform decisions but I  
20 think we should be under no illusion that adults  
21 are necessarily going to be predictive of what  
22 goes on in children, particularly when it comes to

1 not knowing what we don't know.

2 I am going to suggest that maybe we need  
3 to change our perspective from dose exposure  
4 response to perhaps starting with response, moving  
5 to exposure and then to dose and the issue here is  
6 really on determining what is the right exposure  
7 for a given situation rather than just simply the  
8 dose and then finally, I am going to talk a little  
9 bit about some other study designs that we might  
10 want to consider to get information that is  
11 maximally informative in children.

12 So let's look at the population data. We  
13 are going to look at this in two different ways.  
14 The first thing we are going to do is we are going  
15 to look at some of the atomoxetine data that we  
16 generated in a genotype stratified pharmacokinetic  
17 study. What we had available to us was a group of  
18 children who had participated in what we call a  
19 longitudinal phenotyping study and this was a  
20 study in which we administered dextromethorphan,  
21 which is a probe for CYP2D6 activity. We were  
22 interested in how CYP2D6 activity changes as

1 children go through adolescence and so we started  
2 with the population of 7 to 15 year olds and then  
3 we gave them a small dose of dextromethorphan  
4 every six months to see how the CYP2D6 activities  
5 changed. A subgroup of that study population were  
6 about 60-65 children with ADHD and so what we did  
7 was we selected for participation in a  
8 pharmacokinetic study of atomoxetine for children  
9 who were poor metabolizers, had zero functional  
10 copies of the CYP2D6 gene and you'll see this at  
11 the bottom of the screen, an activity score of  
12 zero means zero functional copies of the CYP2D6  
13 gene..5 means they had one chromosome with a  
14 non functional carpula gene and the other  
15 chromosome had a partial function version of the  
16 gene and then the one and two are one functional  
17 copy of the gene and two functional copies of the  
18 gene.

19 Now I am going to talk about systemic  
20 exposure. I think to this audience, I probably  
21 don't need to really describe what I mean by  
22 systemic exposure but I am referring to this

1 concept of area under the curve where we are  
2 looking at changes in blood concentration over  
3 time, with that area under the curve being a  
4 measure of drug exposure and so when we design a  
5 study to look at the consequence of genetic  
6 variation in a gene like CYP2D6, what we will do  
7 is compare the mean plus or minus standard of  
8 deviation exposure in the group that has zero  
9 functional alleles and an activity score of zero  
10 with for example a group that has 1 or 2  
11 functional copies and when we did that in this  
12 particular study, what we found was pretty much  
13 the same as what's reported in the product label  
14 so in the left hand panel, what we are looking at  
15 is roughly a 14 fold difference in the mean value  
16 in the zero functional allele group versus the two  
17 function allele group.

18 Now the dose of atomoxetine that we  
19 administered in this study, this was a single  
20 dosed pharmacokinetic study was 0.5 milligrams per  
21 kilo. Even though there are multiple oral dosage  
22 forms of atomoxetine, it is not possible to give

1 exactly 0.5 milligrams per kilo so what we did was  
2 we figured that pediatricians in the wild would do  
3 and that is to select the single available oral  
4 dosage form that gets closest to a half milligram  
5 per kilo and in that situation, we see that 14  
6 fold range in exposures, however, some of the  
7 variability that we see may be because that there  
8 are differences in the actual dose administered  
9 and in fact it was somewhere between 0.44 and 0.62  
10 milligrams per kilo so if we correct for the dose  
11 that's administered, we can get that variability  
12 down, the mean variability down to 11.4 fold.

13 But from the perspective of precision  
14 therapeutics, I think the insight to us from the  
15 study was when the data are presented like this.  
16 We are looking at each individual participant in  
17 this study because now all of a sudden, the  
18 situation is a little bit different than just a  
19 ten or a fourteen-fold range. That's the  
20 difference in the means. Now we have a situation  
21 where if you look at that in the left hand panel,  
22 the very highest red point, that was the poor

1 metabolizer who had the highest exposure following  
2 a weight based dose, 0.5 milligrams per kilo and  
3 above the two there is a black dot. That was a  
4 participant who had three copies of the gene. It  
5 is actually a 50 fold range in the exposure for  
6 children that were given the same weight based  
7 dose, 50 fold.

8           Now once we do that correction for the  
9 actual dose that's administered, we have that  
10 variability down to 30-fold so this is where we  
11 can start about what precision therapeutics really  
12 means.

13           So let's say that you're the parent of a  
14 child with ADHD and you go into the pediatrician's  
15 office and he or she is going to start you off  
16 with a prescription that has a dose of 0.5  
17 milligrams per kilo of atomoxetine. Where within  
18 that 50 fold range is your child going to fall?  
19 How many times will anybody, when they decide that  
20 a dose adjustment is required will reduce the dose  
21 and not just increase the dose? Do those four  
22 children with the red dots, are they all going to

1 need to have their dose reduced or increased?

2           If they have that high of an exposure  
3 and they haven't responded to the drug, is it  
4 possible that maybe they have a drug target that  
5 will not respond to the drug? These are all  
6 rhetorical questions that we now have to think  
7 about in the context of precision therapeutics for  
8 an individual child. Now ultimately though, what  
9 we are really interested in is whether or not the  
10 child or an adult for that matter is going to  
11 respond to the medication so there are now  
12 commercial services that will provide genotyping  
13 for some genes that are in drug targets and on the  
14 next two slides, we are going to work through a  
15 couple of these.

16           So this is a study that was published in  
17 -- 59 subjects and this is the alpha 2 adrenergic  
18 receptor. It's associated with ADHD but it's also  
19 been associated with the response to  
20 methylphenidate. And so in this particular study,  
21 the P value for the association of a G containing  
22 genotype and clinical response was I believe 0.015



1 and so you can see that there is enough  
2 information in that paper where you can construct  
3 a two by two table and calculate sensitivity  
4 specificity, positive predictive value and  
5 negative predictive value and so one might say  
6 that the sensitivity is 76 percent, maybe not  
7 great but okay but I think where it really gets  
8 interesting is if you start to view this from the  
9 perspective of the clinician who has in his or her  
10 hand a genotype report and let's say that that  
11 genotype report says that the patient in front of  
12 that pediatrician has a genotype that contains a G  
13 allele so the question you are more interested in  
14 is not so much what the sensitivity and  
15 specificity is. What you really want to know is  
16 what is the probability that that child that I am  
17 going to prescribe the methylphenidate to is going  
18 to respond to the drug so that would be the  
19 positive predictive value.

20 On the other hand you might say well  
21 what's the possibility that the child who has the  
22 C allele will not respond to the drug. When we

1 look at the negative predictive value, this is now  
2 a little bit more of a coin flip, it's 50 percent.  
3 So this is a study, you can see the title there,  
4 this is predominantly inattentive type ADHD so  
5 this is pretty good. It's a pretty well defined  
6 population.

7           Now let's look at this study where now  
8 the population is an autistic population with  
9 comorbid ADHD. Look at the sensitivity and the  
10 specificity for the G allele and the positive and  
11 negative predictive value. I don't think -- I  
12 probably don't need to say any more. As it turns  
13 out, the situation is a little bit more  
14 complicated than what I am showing you and that's  
15 because preceding these two studies, there was  
16 another study that had a more heterogeneous ADHD  
17 population and what it showed was that there was  
18 clinical improvement to methylphenidate in both  
19 the G containing genotypes and the C genotype but  
20 you got a faster response in the G phenotype -- in  
21 the G genotype at one month of treatment.

22           So there were subtle differences but the

1 reality is that both genotype groups will likely  
2 respond to the drug, one maybe more than the  
3 other. The only reason that we can construct these  
4 2 by 2 tables is that the response has to be  
5 dichotomized in some way so the way it was  
6 dichotomized in that first study was a responder  
7 was somebody who showed a greater than or equal to  
8 50 percent reduction in the rating scale and then  
9 the other study, this particular study, it was  
10 whether they were classified as much improved or  
11 very much improved by the clinician and then there  
12 was a reduction in rating scales by teachers and  
13 parents so you can get the sensitivity and  
14 specificity if you dichotomize but response is not  
15 really an all or none phenomenon.

16           So if I just summarize this aspect of  
17 the presentation, the challenges in using  
18 population data come from the fact that it is very  
19 difficult to extrapolate population level data to  
20 the individual patient and that is because within  
21 a given genotype within a given genotype group,  
22 there will be some individuals who respond and

1       some who don't respond and what we really need is  
2       prospective validation of the genetic association  
3       data to really get a sense of the true value of  
4       some of these tests.

5                When we look at pharmacokinetic data,  
6       even within a genotype group, there is  
7       considerable amount of variability and we are  
8       going to pursue this in a little bit more detail  
9       in a subsequent slide.

10               We do have these difficulties with some  
11       of the available pharmacogenetic tests in that  
12       they come from relatively small populations so the  
13       two examples that I showed you in the previous two  
14       slides, they had discrepant results. Is this a  
15       function of sampling error because we are looking  
16       at small sample sizes or is it a fact that the one  
17       population used a fairly homogenous subgroup of  
18       ADHD whereas the other one looked at ADHD that was  
19       comorbid condition of autism. But anyway, the  
20       bottom line is that we have to have validation.

21               So competing pathways; we are going to  
22       revisit the atomoxetine data and this time we are

1 going to look separately at the poor metabolizer  
2 group. These are in red symbols and these are the  
3 individuals who have no functional copies of the  
4 CYP2D6 gene and if you look at the spread of the  
5 four red points, what you see is that in a  
6 relative sense, there is really only a two fold  
7 change but in an absolute sense, there is a 35  
8 unit difference in the end of the curb so it's a  
9 really large range of exposures.

10 Same weight based dose, same genotype  
11 but still a broad range of exposures. Now it turns  
12 out that the CYP2D6 generated metabolite of  
13 atomoxetine is 4-hydroxyatomoxetine and when we  
14 look in the urine of poor metabolizer subjects,  
15 4-hydroxyatomoxetine is still metabolite. It's  
16 just that some other P450 is contributing to it  
17 and so in this particular case where the  
18 genetically polymorphic pathway is absent, there  
19 are still other factors that are contributing to  
20 variability and the clearance of that compound and  
21 if we wanted to truly individualize treatment in  
22 this patient group, we have to understand what

1 those other pathways of elimination are. Now if  
2 you look on the right hand panel, where I want to  
3 talk about the EM1 and EM2 groups, these are  
4 individuals with one or two functional copies of  
5 the gene, and that's the cluster of green points  
6 and blue points at the bottom right hand part of  
7 the slide.

8           There is relatively low variability but  
9 there is still relatively large relative  
10 variability and even though those points appear to  
11 be clustered, there is still a four to five fold  
12 range of exposures within that cluster of points  
13 and that's because the scale of the graph is  
14 compressed at that end just because of the  
15 extremely large exposures that we see in the poor  
16 metabolizers so these are individuals who have  
17 relatively similar genotypes but there still is a  
18 relatively broad range of variability, four to  
19 five fold and so there have to be other factors  
20 that are contributing to that four to five fold  
21 range of exposures within that group.

22           One of the things that I didn't mention

1 early on was that when we simulated out the  
2 results of this study to the highest recommended  
3 dose, 1.2 milligrams per kilo, it turns out that  
4 none of those individuals with the green and blue  
5 circles achieved exposures high enough to meet the  
6 threshold of -- in the Eli Lilly literature, there  
7 is suggestion that 800 nanograms per amount is a  
8 threshold above what you see a higher probability  
9 of clinical response. At least this was a  
10 threshold that was used in studies to make a  
11 decision as to whether individual participants in  
12 previous studies would go on to evaluate the  
13 higher doses but anyway, one of the consequences  
14 of this range -- broad range of exposures for a 0.5  
15 milligram per kilo, same weight based dose is the  
16 fact that there are probably a considerable number  
17 of individuals who may not get adequate drug  
18 exposure even at the highest recommended dose of  
19 the medication.

20 This is another example to help  
21 illustrate the importance of looking at competing  
22 pathways. Pimozide is another medication that has

1 not only pharmacogenetic dosing guidelines but  
2 also pharmacogenetic recommendations for children.  
3 And pimozide is an antipsychotic and in children  
4 it's used to treat Tourette's syndrome. There is a  
5 warning for both DDIs and pharmacogenomics in the  
6 label but that CYP2D6 pathway has not been  
7 characterized.

8           This particular figure was taken from an  
9 abstract that was presented at pediatric academic  
10 societies meeting last year and we were very much  
11 interested in the CYP2D6 pathway because it wasn't  
12 characterized in the literature and yet there was  
13 a warning in the product label. As it turns out,  
14 there was a ring hydroxylated metabolite of CYP2D6  
15 generated ring of hydroxylated metabolite.

16           The other pathway that has been  
17 characterized is CYP3A4. Right in the middle of  
18 the molecule, you'll see there is a six membered  
19 ring with the nitrogen, that's where CYP3A4  
20 metabolizes a compound and basically makes two  
21 metabolites that are -- the two halves of the  
22 molecule. But here in this slide, what we are



1 showing is if we look at the sum total of the  
2 CYP3A4 mediated metabolites and the CYP2D6  
3 generated metabolites and express on the Y axis  
4 the percentage of the total metabolite formation  
5 that is represented by the CYP2D6 generated ring  
6 hydroxylated metabolite. What we see is that the  
7 amount of that ring hydroxylated metabolite is a  
8 function of the relative abundance of the CYP2D6  
9 activity to CYP3A4 activity, in this case present in  
10 liver microsomes so at the far end of the X-axis,  
11 going up, there are two blue dots. The two blue  
12 dots mean that those particular samples have two  
13 functional CYP2D6 alleles, they also have 10 fold  
14 higher CYP2D6 activities and CYP3A4 activity measured  
15 using dextromethorphan as a substrate for CYP2D6 and  
16 (inaudible) as a substrate for CYP3A4.  
17 And so almost all of the metabolite  
18 in those two  
19 samples is the CYP2D6 metabolite. At the  
20 other end of the spectrum, there are a couple of  
21 red dots and a green dot down in the bottom left  
22 hand corner. Those are samples, the red dots

1 indicate samples that have no functional CYP2D6  
2 activity and they make very little of the CYP2D6  
3 generated metabolite.

4           So it's not really sufficient to make --  
5 it's really difficult to make decisions regarding  
6 dosing based on CYP2D6 genotype because really the  
7 clearance is going to be a function of the two  
8 pathways that are present there. In the context of  
9 children, we know that genetic variation is more  
10 important than ontogeny or development for CYP2D6.  
11 On the other hand, ontogeny is more important than  
12 genetic variation for the CYP3A4 component and so  
13 it would seem to me that making dosing  
14 recommendations for pimozide in children needs to  
15 take into consideration both of these primary  
16 pathways and not just the polymorphic pathway.

17           So competing pathways then, the issues  
18 are that what we tend to do is to focus on the  
19 polymorphic pathway. We can get away with  
20 atomoxetine but because probably 80 percent or  
21 more of the clearance of the compound is a  
22 function of CYP2D6 but there are other compounds

1       like pimozone where both CYP2D6 and CYP3A4 are  
2       important.

3               There are other examples, for example,  
4       with the proton pump inhibitors where CYP3A4 and  
5       CYP2C19 are responsible for the clearance of the  
6       compound. I think if we are going to get into the  
7       business of precision therapeutics, we need to  
8       look at all pathways and not just the polymorphic  
9       pathway.

10              Furthermore, in the context of  
11       pediatrics, because we also have to think about  
12       developmental trajectories of drug metabolism  
13       pathways, it's going to be really important to  
14       look at those other pathways as well.

15              Extrapolation of adult data to children.  
16       We have within a group a number of pediatric  
17       subspecialists and the data in this particular  
18       slide represented by pediatric cardiologist in the  
19       group, John Wagner, last year, at an AHA meeting,  
20       and what John is interested in is the effect of  
21       genetic variation in the SLC01B1 gene. This is the  
22       gene that codes for the hepatic uptake transporter

1 OATP1B1 and what we were doing, what we were  
2 looking to do is to see if the genotype, phenotype  
3 associations for simvastatin that are observed in  
4 children -- in adults, can be replicated in  
5 children and again, what we are looking at here is  
6 in the simvastatin asset, AUC on the Y-axis on  
7 each of the panels. So simvastatin is administered  
8 as a pro drug as lactone and it has to be cleaved  
9 to the therapeutically active acid. The assumption  
10 is that hydrolysis of the lactone to the acid  
11 occurs quite quickly.

12 In designing this study in terms of the  
13 sampling period, we went along with that  
14 assumption based on the adult literature and we  
15 further assumed that because the clearance of the  
16 simvastatin asset is CYP3A mediated and that CYP3A  
17 activity tends to be a little bit faster in  
18 children than an adult, that we could get away  
19 with an eight hour sampling period. As it turns  
20 out, we were wrong.

21 percent of the kids in that T group,  
22 these are the points that are below the dash line,

1 had basically undetectable or barely detectable  
2 concentrations of the acid. We are also presenting  
3 the area under the curve on the Y-axis as the area  
4 under the curve from 0 to 8 hours and that is  
5 because 8 hours was not sufficient to capture the  
6 terminal elimination phase and that's because the  
7 terminal elimination phase was flat in many of the  
8 kids and certainly was not -- didn't have enough  
9 pitch to it for us to calculate a half-life.

10 That type of situation occurs when, for  
11 example, conversion of the lactone to the acid is  
12 very limiting and what it suggested to us is that  
13 perhaps one of the assumptions that we made based  
14 on adult data, that conversion or hydrolysis of  
15 the lactone to the acid was rapid, was incorrect.

16 Unfortunately, there is not a lot of  
17 good information on what enzyme systems catalyze  
18 the hydrolysis of the lactone to the acid. Some  
19 obvious candidates are the carboxylesterase, these  
20 don't appear to be the case but there is another  
21 group of enzymes called the paraoxonases that may  
22 be responsible for the cleavage so now we've got a

1 lot of work to do, we need to start to -- we need  
2 to map out the pathways responsible for hydrolysis  
3 of the lactone to the acid so that we can start to  
4 figure out what's going on in children but the  
5 implications of this are that 25 percent of the  
6 kids who at least in this study who were given a  
7 single dose of simvastatin do not have detectable  
8 concentrations of the pharmacologically active or  
9 therapeutically active acid. Now we don't know  
10 what the implications of that are. If you look,  
11 six of the seven -- there were 28 children who  
12 participated in the study. Six of the seven were  
13 in the TT group; this is the group that has  
14 functional -- most functional transporter  
15 function. It's quite possible that those children  
16 have low systemic concentrations because the drug  
17 has made its way into the liver but we don't know  
18 that so we are not going to be able to conduct the  
19 studies looking at the efficacy of simvastatin in  
20 dyslipidemic children until such time as we have a  
21 better handle of what's going on with the drug.

22 So the concept of right exposure. So

1       again, I think we need to think, sit back, kind of  
2       close our eyes and think about the clinical  
3       situation that practitioners face and that is if  
4       you are going to prescribe a medication to the  
5       child, probably what you really really want to  
6       have happen is that the child respond to the  
7       medication with a reduced risk of toxicity. So  
8       really what's driving the decision is the response  
9       so then the question ought to be well what  
10      exposure do I need? How much drug do I need to  
11      have in the body to increase the probability that  
12      I am going to get the response that I want while  
13      reducing the risk of the toxicity that I don't  
14      want.

15                   Now in this age of precision  
16      therapeutics, what dose do I need to administer to  
17      that child to get that exposure to get the  
18      response that I want so this is why I find this  
19      quote from John Maynard Keynes so very appropriate  
20      for the situation that we are facing now at  
21      precision therapeutics. "The difficulty lies not  
22      so much in developing new ideas as escaping from

1       our old ones." The fact that we are working to  
2       find out what the right dose is -- we already know  
3       that for drugs that are subject to pharmacogenetic  
4       polymorphisms, the same dose, even the same weight  
5       based dose can give us as much as a 50 fold range  
6       in exposures so what's the right dose for that  
7       child, the red symbol in the atomoxetine slide that  
8       was at the very very top and what's the right dose  
9       for the black dot that was at the very very bottom  
10      at the lowest exposure. If only it were that  
11      simple. So this is a slide that I took from a  
12      paper that basically pulled the results of the  
13      atomoxetine trials that were submitted to the FDA  
14      for approval and in this particular analysis, they  
15      observed that there was a group of children, the  
16      diamonds that go along the top, that had a very  
17      modest reduction in the ADHD rating scale over the  
18      nine week course of these studies.

19                    On the other hand, there was another  
20      group that had a very robust response over the  
21      nine week trial. Now there are no arrow bars here  
22      so we don't know how much variability there is and



1 we don't know how much overlap there is but those  
2 children that are classified as non-responders,  
3 given what we now know about the variability and  
4 exposure, even with the same weight based dose,  
5 and the results of our simulations that suggest  
6 that maybe there is a subset of the population  
7 that even at the highest dose won't have adequate  
8 exposures, how do we know -- how can we tell the  
9 difference for those individuals who did not  
10 respond to the medication, was the fact that they  
11 didn't respond, was that a consequence of the  
12 inadequate exposure or is there something  
13 functionally different about the drug target?  
14 Either related to ontogeny, maybe it's not  
15 expressed, we don't know anything about the  
16 developmental trajectory of the norepinephrine  
17 reuptake pump or is there something different --  
18 is there genetic variation affecting the coding  
19 region of the gene that affects transporter  
20 function? How can we differentiate between lack of  
21 responses due to inadequate exposure from genetic  
22 variation in the drug target or developmental

1 differences?

2                   So this is just a cartoon to help you  
3 with this particular concept. So on this  
4 particular slide, I've got three dose response  
5 curves that are shifted two-fold. The warfarin  
6 minus 1639 variant that's in the label, the  
7 warfarin label, when you look at the original New  
8 England Journal of Medicine article, it had about  
9 -- each copy of the variant VKORC1 allele was  
10 associated within 1.8 to 2 fold change in  
11 expression on average of the drug target so here  
12 we've got three dose response curves that are  
13 shifted by a factor of two fold. That shaded area,  
14 the grey shaded area, let's say it's our  
15 therapeutic target. We want to reduce the -- we  
16 want to have a target response that's somewhere  
17 between, let's say 30 something and I guess you  
18 can -- I can see it better on that one over there  
19 in the distance than I can but I'll describe it  
20 for the people who can't see the grey shaded area  
21 because I can't see it on my screen here either  
22 but it's somewhere in the 30 percent to maybe

1                   percent range so let's say we want a  
2                   response that reduces the activity of whatever  
3                   this thing is to within 35 to 60 percent.

4                   For each of the curves, the red curve,  
5                   the green curve and the blue curve, what I've done  
6                   is I've dropped dotted lines down where that  
7                   shaded area hits each of those response curves and  
8                   at the very bottom, the red and the green and the  
9                   blue rectangles represent the concentration range  
10                  that each drug target genotype group would have to  
11                  be within to have the same clinical response.

12                  (Track 36 concludes)

13                  DR. LEEDER: This is something that we  
14                  really don't think about right now is if we are  
15                  going to focus on variability and drug response,  
16                  we should be starting to think about genetic  
17                  variation and ontogeny as it influences the  
18                  expression of the drug target. Because if we have  
19                  differences in the amount of drug target that's  
20                  available we don't necessarily all need the same  
21                  drug exposure.

22                  And then we're going to have to

1 individualize the dose so that we each get our own  
2 individual drug exposure. That is if we really  
3 are serious about precision therapeutics.

4           So just to summarize, when we think  
5 about things right now we administer a medication,  
6 a drug for a clinical trial for example, there is  
7 a drug response phenotype that's usually  
8 classified as a responder, or a non-responder, or  
9 a partial responder. And for that non-responder  
10 group, it's without actually measuring to see  
11 where we are with exposure in a clinical trial, we  
12 really don't know whether that lack of response,  
13 that non-response, is a function of inadequate  
14 exposure. It might occur for the pharmacokinetic  
15 things that I've been describing right now. It  
16 might also occur for adherence. But we try to  
17 take into consideration adherence in clinical  
18 trials. But we also don't know if non-response is  
19 actually a consequence of low level of expression  
20 of the drug target, or its absence, or some sort  
21 of functional change in the structure of the drug  
22 target that is associated with an inability to

1       respond. We don't know.

2               So similarly, even if we were to have  
3       knowledge of the level of drug target expression,  
4       we really need to start to collect the information  
5       on what drug exposure is required to elicit that  
6       desired response. And then the real challenge is  
7       to figure out how to individualize the dose for  
8       that individual so that we can get to that target  
9       exposure.

10              And so now I'm going to finish up here  
11       in the next five minutes with just giving you some  
12       thoughts. It's my opinion, nothing else, as to  
13       how we might go about collecting some of this  
14       information. And so I think before we get to that  
15       we really need to consider where we've been, and  
16       where we want to go. We've gone through the age  
17       of personalized medicine and I like to think of  
18       this, I haven't pulled this from anywhere. This  
19       is just my trying to rationalize how we've gone  
20       from personalized medicine to individualized  
21       medicine to precision medicine, and I've heard  
22       personalized medicine described as describing the

1 encounter between patient and physician. And I  
2 know that I have reached the age and I have a  
3 family history that makes it imperative for me to  
4 have a very personal encounter with my physician  
5 every year. My wife tells that's nothing, that  
6 she has personal encounters that are worse than  
7 that.

8           But individualized medicine takes us  
9 into the situation where we are starting to use  
10 information that is unique to the individual to  
11 help make the decisions, and hence the transition  
12 to individualized care. But now we have at our  
13 disposal vast amounts of information that comes  
14 from [3:45 OMIC] technologies, that now really  
15 allow us to venture into the realm of precision  
16 medicine which can be broken down into precision  
17 diagnostics. We use this in the NICU at our  
18 institution for rapid diagnosis of genetic  
19 disorders in the NICU. But with that information  
20 also comes the pharmacogenome, for example, that  
21 can be used to start to inform decisions and bring  
22 us closer to precision therapeutics.

1                   So I think our experience with the  
2                   Strattera study has really pushed us towards the  
3                   genotype stratified pharmacokinetic study design.  
4                   And, as I mentioned, Dr. Wagner, the young  
5                   cardiologist in our group, he is using a similar  
6                   design, SLC01B1 genotype stratified  
7                   pharmacokinetic studies. I showed you the  
8                   [Simvastatin] study. We have he's finished a  
9                   pravastatin study. We're writing it up now. And  
10                  we'll be finishing up a atorvastatin and  
11                  rosuvastatin study probably within the next six to  
12                  nine months.

13                  But it turns out that if you have at  
14                  your disposal a patient registry, so there's some  
15                  patient related information that is coupled with a  
16                  DNA repository, and IRB approval, where in the  
17                  permission and assent form you have parental  
18                  permission and patient assent to contact  
19                  individuals for future participation in the study,  
20                  that it can be a fairly efficient design to  
21                  genotype your repository and invite participants  
22                  to come back for a study once you know what their

1 genotype is. And this is what we've done.

2                   What this does is to allow us with a  
3 sample size of to 28 subjects, for example, to  
4 have a better chance of

5                   capturing the extremes of the  
6 population. Because you can select for  
7 participation those individuals who have zero  
8 functional alleles and those individuals who have  
9 two or more. And then to the extent to which you  
10 want to fill in in between, you can start to get a  
11 richer data set.

12                   So in our particular situation with the  
13 Strattera study we chose individuals with zero  
14 functional alleles, at the other end of the  
15 spectrum two functional alleles, and then filled  
16 in with one and ).5. Now, you can see it's also  
17 possible to have a genotype that has on one  
18 chromosome a fully functional allele and a partial  
19 function, so we could have a 1.5 group if we  
20 wanted as well. Or if we had the money to do the  
21 study.

22                   But the value of this, there's two



1 values. One is that we have a better chance of  
2 capturing the extremes of the study of the  
3 population. One of the other things it does is  
4 create a dataset to build some models that might  
5 allow us to individualize. But before we get to  
6 that, I want to introduce the concept of a  
7 genotype stratified pharmacokinetic study. And in  
8 this type of study once we know what the drug  
9 target is and we have an idea of genetic variation  
10 in the drug target, so the two little vignettes I  
11 gave you near the beginning of the talk with the  
12 alpha 2 adrenergic receptor, that is a drug target  
13 for a methylphenidate, for example. We could  
14 technically stratify by drug target genotype. We  
15 need to recognize that some genetic variance, if  
16 they occur in the regulatory region of the gene,  
17 may determine the level of expression. Whereas  
18 genetic variance in the coding region may modify  
19 function, but linkage disequilibrium across a  
20 locus may result in haplotypes involving both  
21 types of genetic variant.

22 Now, here comes the kicker though, if we

1 are going to stratify the patient population by  
2 drug target genotype, we can't give everybody the  
3 same dose. If we gave everybody the same dose of  
4 atomoxetine, we would have a 50 fold range of drug  
5 concentrations in each of the three groups. So  
6 what are the changes that we would be able to  
7 discern the effect of genetic variation in the  
8 drug target when we have a 50 fold range, or a 30  
9 fold, or even a 10 fold range of exposures?  
10 Probably can't. So what we have to be able to do  
11 then is give everybody the same exposure, the same  
12 amount of drug in their system. So how are we  
13 going to do that? Well I don't know if you can  
14 see this on your monitors. You can't barely see  
15 it here. But anyway, this is what we've been  
16 doing. We are now trying to use the data from the  
17 genotype stratified pharmacokinetic study to build  
18 what are in essence population pharmacokinetic  
19 models that would allow us to individualize the  
20 dose to get to a common exposure. And right now  
21 in preparation for that U54 study we are  
22 validating this model to see how well we do.

1 We've done four subjects so far and it's a little  
2 early to tell how well we are doing with this  
3 dosing algorithm, but it is my opinion, it's our  
4 opinion that if we are going to get at the issue  
5 of variability and drug response, which is  
6 ultimately what we want to do, we've got to have  
7 this type of data and we're going to have to have  
8 these types of tools to conduct the studies.

9           So all this is encompassed at our  
10 institution, a program we call GOLDILOKS,  
11 philanthropy loves it, because it's not too  
12 difficult to explain to a donor what clinical  
13 pharmacology does if you couch it in not too big,  
14 not too small, the dose of medication that's just  
15 right for your child. And if that doesn't bring  
16 out your checkbooks, I don't know what will. But  
17 anyway, it is in essence what we are trying to do  
18 with do with pediatric precision medicine, is to  
19 use those features that make each child unique,  
20 their genome, and their stage of development, and  
21 integrate those with other patient related  
22 information to come up with the dose that's just

1 right.

2           And I believe that the focus here needs  
3 to be on the drug response, and we need to have  
4 these tools that allow us to administer a dose  
5 that gives a constant exposure if we are ever  
6 going to get at that endpoint.

7           So I have abused my privilege by about  
8 ten minutes. But this is the last slide.  
9 Basically this just reiterates everything that  
10 I've said. I said in the very first point there  
11 were three issues. I think we need to have  
12 studies that look at validating in a prospective  
13 manner anything that we are going to use to  
14 information decisions involving the response of a  
15 child to a medication. I think that the models  
16 that we've develop to do this need to be more  
17 comprehensive and focus beyond just the  
18 polymorphic pathway. The polymorphic pathway is  
19 the low hanging fruit. Precision therapeutics  
20 means that we need to have a more comprehensive  
21 view of things. And I think it's really important  
22 to generate the data in the patient population

1       that's going to receive the drug.

2                   And so one could argue, there are those  
3       who will say well you can't study the medication  
4       in kids. And I would argue if you're going to  
5       give the medication to kids, why can't you  
6       generate the data that's going to ensure that  
7       using that drug is going to be safe and effective.  
8       Again, if the goal is drug response we need to  
9       focus on the ontogeny and genetic variation of  
10      drug targets, not just the drug metabolizing  
11      enzymes. After all, the proximal phenotype for a  
12      cytochrome P450, is not drug response, it's how  
13      much metabolite is formed. And from the how much  
14      metabolite is formed, we infer the exposure to the  
15      pharmacologically active compound. But the focus  
16      needs to be on the drug target.

17                   And I'm not going to belabor the  
18      potential value of genotype stratified  
19      pharmacokinetic studies or genotype stratified  
20      pharmacodynamic studies to generate the data that  
21      we need. So we are still around 20 minutes before  
22      the break. So I took kind of 40 minutes, rather

1       than 30.

2                   DR. HUDAK: That's okay. Very good. So  
3       I think everybody has been bombarded with a lot of  
4       different information here. And we need to take a  
5       20 minute break to digest and come back. So we're  
6       looking at let's say 3:20.

7                   [FILE 38]

8                   DR. HUDAK: We will reconvene. Give  
9       everybody a minute or two to get to their seats.  
10      And if we could have the first slide on the  
11      questions put up. Great.

12                   So we are allotted two hours for the  
13      discussion to discuss two questions. I think  
14      we'll just have to see how it goes. So in any  
15      case the first question, I'll read it for the  
16      record. Based on your clinical experience and the  
17      information provided to you at this meeting,  
18      please discuss the role of pharmacogenomic testing  
19      in your care of patients. So we all come from  
20      many different units, in-patient, outpatient,  
21      etcetera, there's a lot to discuss.

22                   In this discussion please consider the

1 following topics: situations that merit ordering a  
2 pharmacogenomic test before prescribing a  
3 medication; the challenges that may arise in  
4 obtaining and/or using this information;  
5 situations where you would request a  
6 pharmacogenomic test to explore an association  
7 with a serious adverse drug effective experience  
8 by a patient; and finally the source or sources of  
9 pharmacogenomics information that you and other  
10 pediatric practitioners may use to inform your own  
11 clinical practice, so that's quite a mouthful.

12 But I guess we'll start. So who's ever  
13 brave enough to begin the discussion. I'm looking  
14 at Dr. White, but he had said that he has figured  
15 this all out but he was so confused by the [end  
16 2:05] that he was going to hold comment for a  
17 little while. So somebody else can have the  
18 privilege.

19 DR. JONES: I'll start. It's Bridgette  
20 Jones, and Dr. Leeder is actually my division  
21 chief, so I may have a little bit more information  
22 to discuss this topic. I just really want to talk

1 about, so in our division one of the things Dr.  
2 Leeder mentioned was that we have several  
3 pediatric specialists that are cross trained in  
4 clinical pharmacology. And so we have utilized  
5 those staff to start an individualized pediatric  
6 therapeutics clinic. So I'm one of those people  
7 that get to see the patients after they have  
8 genotyping and try to explain their results to  
9 them and try to help the practitioners to  
10 understand those results and make dosing  
11 recommendations. And I think that Dr. Leeder did  
12 a good job of point out a lot of the difficulty  
13 that we encounter in trying to translate genetic  
14 information into dosing in those children.

15 A lot of the children that are referred  
16 to our clinic are ADHD patients. So we deal a lot  
17 with drugs like atomoxetine and other drugs that  
18 are metabolized by CYP2D6. And I think that in  
19 trying to guide parents and guide practitioners  
20 one of the things that Dr. Leeder pointed out was  
21 the variability, if you have a poor metabolizer,  
22 what does that mean. When you saw those bars in



1 the poor metabolizer group there's a lot of  
2 variability in that group. And so we struggle  
3 with trying to translate that into a dose  
4 recommendation for the provider and for the  
5 parents.

6           Sometimes we will recommend that they  
7 choose a different medication that's metabolized  
8 by a different pathway that it doesn't appear that  
9 they have genetic variant. They may affect  
10 response and sometimes we may recommend that they  
11 use a higher dose or a lower dose. But I think a  
12 lot of times practitioners are looking for more  
13 specific information. And so with the variability  
14 that's seen among poor metabolizers or  
15 intermediate metabolizers and also with taking  
16 into consideration of other factors, like are  
17 there transporters involved, are there other  
18 pathways involved, and also is it really just  
19 genotype of your drug metabolizing enzymes, but  
20 also we need to look at the target, the receptor,  
21 it makes it difficult sometimes to make specific  
22 recommendations.

1                   And so in looking at the labeling for  
2           atomoxetine it discusses that there are  
3           differences in genotype that may affect response,  
4           but I feel like those recommendations are pretty  
5           general. And so if a practitioner is using the  
6           label for dosing or for recommendations on how to  
7           start a patient, I'm not sure that those  
8           recommendations are that helpful a lot of times.  
9           And I think that's why we end up seeing them a lot  
10          of times in clinics when they get those genotype  
11          results back.

12                   The other point I'd like to make was  
13          also in looking at the label was it discusses that  
14          approximately 7% of the Caucasian population are  
15          poor metabolizers and it doesn't mention any other  
16          racial or ethnic groups. So if you have a patient  
17          that's not Caucasian I don't know what you're  
18          supposed to make of that statement. So does that  
19          mean that everyone else is normal, or... So some  
20          further guidance at least including what's known  
21          in other ethnic populations I think may be helpful  
22          if you're going to include it in the label and

1 all.

2 And I think that was all of my comments.

3 DR. HUDAK: Do Dr. Havens, you have a  
4 comment on the phone? If you do you are on mute.  
5 Okay, we have lost Dr. Havens for the moment. Is  
6 he connected, do you know? Okay.

7 All right. Dr. Sayej.

8 DR. SAYEJ: Thank you. Thank you for  
9 the wonderful presentations this afternoon by Dr.  
10 Green, Michael, Dr. Kelm, and Dr. Leeder. Very  
11 informative and very helpful in terms of figuring  
12 out what to do with this. I remember the last  
13 time I was here in September we had the discussion  
14 about one of the medications and whether genetic  
15 testing prior to starting the medication should be  
16 added to the label of the drug or not.

17 We all encounter this in our practices,  
18 no matter what the specialty is. I'm a pediatric  
19 gastroenterologist and there are several drugs  
20 that we use that it would be helpful for us to do  
21 genetic testing on these patients to see what kind  
22 of metabolizers they are before we start the

1 medication. Unfortunately, we're not always able  
2 to do that. Insurance companies are not covering  
3 some of these tests and whether it is on the label  
4 or not, we've run into some issues in the past  
5 with that. I'm not sure if that's still the case  
6 or not. But there are some drugs that we  
7 completely stopped using because of that reason in  
8 the past.

9           The day of personalized medicine is here  
10 for sure. But I don't know if pharmacogenomics  
11 testing is ready for that primetime exposure yet.  
12 We have the capabilities of doing it. I'm not  
13 sure if we have the commercialization aspects in  
14 place and the healthcare economic implications of  
15 these tests are unmeasured. So we don't know what  
16 the impact will be in terms of how many tests do  
17 we need to do in order to detect one that will,  
18 for example, tell us that this patient is going to  
19 have an adverse event. Again, this is all  
20 speculative right now. I'm not making any direct  
21 statements, but I think we need to take these  
22 things into consideration as to whether we will

1       decide at the end whether this is something that  
2       needs to be on every label or not.  And what  
3       impact will that have on the clinical practice,  
4       and what impact will that have on physicians who  
5       are trying to prescribe these medications and who  
6       are probably not well educated on what these tests  
7       actually are, where to order them from, where to  
8       send patients to get these tests done, who's going  
9       to pay for these tests, are the insurance  
10      companies going to pay for them, or are the  
11      pharmaceutical companies going to pay for them, so  
12      there are a lot of things that are not in place  
13      yet for us to say that this is ready for  
14      primetime.

15                   DR. HUDAK:  So thanks.  I'll echo a  
16      couple of those thoughts.  So Dr. Leeder, the  
17      issue of cost and approval and so forth is a real  
18      one, and that will vary sometimes from payer to  
19      payer.  So I think you're right.  I think we're  
20      not at the point where for a lot of these things  
21      we can just order a test and expect it'll be done,  
22      even though it may be helpful and informative.

1           I was curious whether you could tell us  
2           a little bit about the penetrance of this across  
3           children's hospitals. I'm familiar with some  
4           hospitals, like for instance, St. Jude's. People  
5           at St. Jude's wrote an article about a year ago  
6           where they described their results with their what  
7           they called the pharmacogenomics for kids. I  
8           think they tested about 230 pharmacogenes. This  
9           project was grant funded, or foundation funded.  
10          So they tested all of these different things that  
11          could contribute to variability in efficacy for  
12          certain drugs or in safety. And they made the  
13          comment that over the course of a year a very high  
14          proportion of children that came to their hospital  
15          for treatment had at least one drug that was a  
16          pharmacologically important one in terms of the  
17          genotype.

18                 So I don't know to what extent this is  
19          propagated. You're sort of on the leading edge of  
20          things, I understand, but maybe you could give us  
21          a little bit more background as to the practice  
22          across the country for children's hospitals.

1 DR. LEEDER: I can give you very  
2 accurate numbers concerning penetrance. Certainly  
3 St. Jude has a program and the genotyping they do  
4 is I believe on the [DMET 11:42] chip. The  
5 University of Wisconsin I believe does the  
6 genotyping for them. Austin Children's has a  
7 genotyping program. We do not have a preemptive  
8 genotyping program. Our genotyping is what I  
9 would say more forensic, as Dr. Jones has  
10 described in our individualized pediatric  
11 therapeutics clinic.

12 We will eventually move to a preemptive  
13 genotyping program. But one of the knowledge  
14 deficits that really prevents us from jumping at  
15 such a program is just what Dr. Jones had  
16 indicated is that given the variability that we  
17 have seen between genotype groups for example, we  
18 think that unless we can provide the practitioners  
19 with useful information, we really can't do  
20 anything in a preemptive way. So that's what  
21 we're trying to do right now with the various  
22 studies that I described is to start to generate

1 the knowledge base that might help to inform  
2 what's going on.

3           The information that is available to  
4 institutions, pediatric institutions who want to  
5 implement pharmacogenetics, the CPIC guidelines  
6 some of them have a little bit of pediatric  
7 information in them. Sometimes the pediatric  
8 information is that we don't have any pediatric  
9 information. But I believe the SSRI CPIC  
10 guideline has information at least for CYP2D6  
11 there were it's reasonable to expect that whatever  
12 genotype phenotype associations are seen in adults  
13 is probably applicable to kids. Because beyond a  
14 year of age for example, the pathways pretty much  
15 mature.

16           I'm trying to think. The CYP3A5  
17 tacrolimus guideline I think has a little bit of  
18 pediatric information in it, because there are  
19 pediatric data. Of course there's the codeine  
20 one, but this committee has already made a  
21 recommendation regarding codeine. But beyond that  
22 there's not a lot of pediatric information that



1 somebody who wanted to implement a preemptive  
2 genotyping program in a pediatric institution  
3 could really use.

4 DR. HUDAK: Sir, for the  
5 transcriptionist, could you define what CPIC  
6 stands for?

7 DR. LEEDER: Yeah. C-P-I-C, clinical  
8 pharmacogenetics implementation consortium.

9 DR. HUDAK: Okay. Dr. Kishnani, you  
10 have a comment. Are you on mute? Are you getting  
11 e-mails? Okay. Issue, all right. We'll  
12 wait until we get that cleared up. Yes?

13 DR. KASKEL: So I too liked to thank all  
14 the presenters for a mini education course into  
15 the new medicine. I'm Rick Kaskel. So I wanted  
16 to ask about the concept of applying some of these  
17 methods across the lifespan with special  
18 populations at risk. So there are some examples  
19 now of certain alleles that place special  
20 populations at risk for conditions and lack of  
21 response to therapies. One in particular starts  
22 with women of African-American background who have

1 preeclampsia. And in several special population  
2 studies those that carry to the 2G risk alleles  
3 for the [APEL 15:53] L1, 1 and 2, are prone to  
4 preeclampsia, prematurity, low birth weight.  
5 Their offspring, if they carry both alleles are  
6 prone to genetic abnormalities of the kidneys and  
7 acquired glomera diseases and hypertension, and  
8 CKD.

9           Across the lifespan into the adolescent  
10 and young adult those African-Americans with two  
11 risk alleles are prone to HIV nephropathy,  
12 diabetic nephropathy, and obesity related kidney  
13 failure. I don't know if anyone's looked at the  
14 third generation, the grandparents, but I suspect  
15 that that's waiting to be done.

16           So here's an expression of phenotype of  
17 risk alleles in a special population that may  
18 require special second and third hits, or  
19 epigenetic signals that will effect response to  
20 therapy or development of a disease process. And  
21 it offers an opportunity to really think about how  
22 you would study this across the lifespan and apply

1       some of the information to registry a databank  
2       knowledge to see how we could apply precision  
3       medicine to this special population.

4                   DR. HUDAK: Dr. Zuppa.

5                   DR. ZUPPA: Hi, it's Athena. And I want  
6       to thank everybody too. So I work at [JOP 17:21]  
7       and I work in the ICU and on average one of our  
8       patients is on 15 drugs, 20 drugs at a time. We  
9       have to build pumps to put on top of the pumps.  
10      And none of this applies in the ICU. I mean I  
11      don't even know how to get access to it. And I  
12      think it's important all around, but if you look  
13      at a drug like tacrolimus or tacrolimus  
14      [pronounced differently], you can do therapeutic  
15      drug monitoring for that to some extent.

16                   If you did look at a drug like  
17      [badazelam 17:53] that's hydroxylated and then  
18      glucuronidated and then excreted, you know the 1  
19      4 hydroxy metabolite is active. Whole bunch of  
20      talk out there about how GABAergic stuff is  
21      neurotoxic and these kids aren't clearing it. We  
22      don't do therapeutic drug monitoring for it. We

1 kind of are they too sleepy? Are they not sleepy  
2 enough? So if there's an area or two, and I may  
3 make a plug for myself, it's drugs that we can't  
4 do TDM for and don't forget about the critically  
5 ill child.

6 DR. HUDAK: So let's parse the question  
7 down a little bit more specifically then. So  
8 given the range of practices we have are there any  
9 drugs right now that you would seriously consider  
10 after hearing the presentations today looking  
11 into, at least, getting a pharmacogenomics test to  
12 inform your further therapy of a patient?

13 DR. ZUPPA: If --

14 DR. HUDAK: Dr. Zuppa.

15 DR. ZUPPA: If I won the lottery and I  
16 could have anything that I wanted or?

17 DR. HUDAK: We'll get to the second part  
18 of the question later. So yes, if you won the  
19 lottery.

20 DR. ZUPPA. Okay.

21 DR. HUDAK: Dr. Kaskel.

22 DR. KASKEL: I would start with one of

1 the oldest drugs that we have available, and that  
2 would be corticosteroids, which we use for a lot  
3 of conditions. This would go back to the 1950s.  
4 But I would look at steroids with changes in  
5 receptor mechanism, post receptor signaling,  
6 et cetera. But we know that some children respond  
7 and some don't. And we get a lot of toxicity when  
8 we give it in excess. And if we knew beforehand  
9 that they were not prone to respond, we wouldn't  
10 use that agent.

11 DR. ANNE: Actually another one would be  
12 warfarin. I have a 15-month old one who had  
13 mitral valve replacement with a prosthetic valve,  
14 and he's on that. And then I have another  
15 five-year old with aortic valve replacement. All  
16 three of them respond very differently. The five-  
17 and the 15- year old are actually relatively  
18 stable. However, this 15- month old is all over  
19 the place.

20 You know the parents maintain that the  
21 diet is relatively stable, because they are  
22 controlling what she's eating. However, it's the

1 same dose and even the smallest change, like a  
2 half a milligram change in the daily dosing. One  
3 time dose change is leading to a significant  
4 change in the INR. So it's very perplexing. It's  
5 very tough. I'm unfortunately having to poke the  
6 patient a number of times a month to figure out  
7 how to adjust this. It's a constant battle.

8 DR. HUDAK: Dr. Sayej.

9 DR. SAYEJ: I would add some of the  
10 newer most expensive medications that we have out  
11 there biologics, there are patients who are  
12 primary responders. There are patients who are  
13 primary non-responders. And there are patients  
14 who respond initially then they lose response.

15 We also know that children under five  
16 years of age don't respond typically well to these  
17 medications because this is an inflammatory bowel  
18 disease, I'm referring to, because they have other  
19 genetic alterations that are probably predisposing  
20 them to a more severe disease and preventing them  
21 from responding to the medications.

22 The other medication that I referred to

1 earlier that wasn't really covered by insurance  
2 was 6-mercaptopurine which now has a black box  
3 warning about use in young adolescent males due to  
4 the development of a deadly form of lymphoma  
5 called Hepatosplenic T-cell lymphoma, so therefore  
6 we no longer use that medication in young males  
7 with inflammatory bowel disease.

8 DR. HUDAK: All right. Dr. Havens,  
9 we'll try again.

10 DR. HAVENS: Thank you. Time for me to  
11 talk?

12 DR. HUDAK: Yes, please.

13 DR. HAVENS: Perfect. I think we have  
14 the phone line fixed now and I appreciate the  
15 prior discussion. There's two issues about the  
16 GOLDILOKS conceptualization. Let me get my  
17 computer unmuted, it'll make me crazy. So the  
18 first is the generic variation which was very well  
19 discussed by Dr. Leeder, but the prior discussant  
20 also talked about ontogeny which Dr. Leeder  
21 pointed out as an important issue. And in the  
22 discussion of valproic acid made it clear that the

1 difference in toxicity in adults is 1 in 10,000  
2 where in children it's 1 in 55. And you know when  
3 we started this discussion with the [fabrins  
4 23:46], you notice that we were careful to only  
5 focus our restrictions in children under three  
6 where the genetic effect seems to be strongest and  
7 that kind of age related change in clearance, for  
8 example, is also seen in other drugs some of which  
9 others might use like cyclosporine.

10 So the reason I can't be ready to be use  
11 pharmacogenomics in pediatrics is because of all  
12 the issues that have been raised in terms of not  
13 enough population data, not enough data  
14 specifically in children to understand, but also  
15 because you need to understand how the genetic  
16 effect changes by age. And so I wonder if Dr.  
17 Leeder or Dr. Pacanowksi could elaborate on that  
18 a little bit, because for us in the [efabrin  
19 24:56] think that was one of the driving factors  
20 here.

21 DR. HUDAK: That's the delay in the  
22 webcast I assume.



1 DR. LEEDER: Okay. Steve Leeder. Yes,  
2 Dr. Pacanowski had kindly deferred. Thank you.  
3 I think the issue it's hard to argue with those  
4 sentiments. It's hard to implement  
5 pharmacogenetic based dosing in children in the  
6 absence of evidence basically. And that's the  
7 whole purpose of our group is to start to generate  
8 the evidence.

9 I think in terms of the cytochromes P450  
10 it's fair to say that we can anticipate adult  
11 relationships in terms of genotype, phenotype  
12 associations once we know that the expression of  
13 the particular pathway has fully matured. I think  
14 we have a pretty good sense of that from most  
15 P450s right now.

16 In many cases we get that information  
17 from pharmacokinetic studies that are conducted in  
18 younger children with medications that are thought  
19 to be prototype, if you will, substrates of the  
20 particular pathway. So what I'm really thinking  
21 about as an example would be proton pump  
22 inhibitors like Pantoprazole there's pretty good

1 pharmacokinetic data in neonates now, and neonates  
2 that have been genotyped for cytochrome P452 CYP2C19  
3 where the data imply or suggest that that genotype  
4 phenotype association that poor metabolizers of  
5 cytochrome P452 C19 start to declare themselves  
6 around five months postnatal age. When you look  
7 at the PK data and that data set I'm referring to  
8 I believe Bob Ward from the University of Utah was  
9 the first author on the papers, but basically the  
10 CYP2C19 poor metabolizers in terms of apparent  
11 oral clearance were indistinguishable from  
12 neonates of the same age in that age group that  
13 was sort of less than say two or three months old.

14           And everybody looked like a poor  
15 metabolizer basically because the pathway hadn't  
16 turned on yet, but you start to see a separation  
17 once you get out five or six months. But  
18 basically that's where the information comes from.  
19 The most useful in vivo data come from  
20 pharmacokinetic studies of compounds where the  
21 metabolic pathway's been pretty well mapped out.  
22 And we have a good idea of what's going on.

1                   And so I guess to start to get the  
2                   information that helps us know when  
3                   pharmacogenetic relationships might be of use to  
4                   us would be to have more of these pharmacogenetic  
5                   data accompanied by genotyping so that we can look  
6                   at genotype, phenotype relationships as a function  
7                   of age. But until we have the data it makes it  
8                   very difficult to know exactly what to do.

9                   DR. HUDAK: Thank you. I think we have  
10                  Dr. Kishnani back for a comment.

11                  DR. KISHNANI: Yes. Can you hear me?

12                  DR. HUDAK: Yes, very well.

13                  DR. KISHNANI: Thank you. So my comment  
14                  was in the field of chemical and biochemical  
15                  genetics. We have come into situations of  
16                  patients who are prescribed carbamazepine or  
17                  Dilantin for seizure disorders. And clearly there  
18                  is an association we know with certain HLA  
19                  subtypes, I think it's HLA B1502, in the Asian  
20                  population. And we have encountered two or three  
21                  life-threatening situations of Stevens-Johnson  
22                  syndrome in patients here of Asian descent who

1 clearly were put on the drug and had this  
2 life-threatening reaction.

3 But in trying to be a good citizen and  
4 do it for the future, we've hit the roadblocks of  
5 difficulties with insurance or in timing of how to  
6 get this done, et cetera. So just wanted to raise  
7 this as a point. The same has come about also  
8 with allopurinol which we use for many of our  
9 patients with the hyperuricemia states, like in  
10 the glycogen storage diseases. And I've hit the  
11 same challenge with Stevens-Johnson syndrome of  
12 really dangerous drug rash. So I'm completely on  
13 board and would like to find a way where we can  
14 make this safe. It's not just a question of even  
15 dosing, but it's really a question about safety  
16 here.

17 DR. HUDAK: Dr. Callahan and then Dr.  
18 White.

19 DR. CALLAHAN: David Callahan. I think  
20 some of these drugs need to just go away. I'm a  
21 neurologist. Haven't prescribed Dilantin the 30  
22 years I've been in practice. Haven't prescribed

1 carbamazepine in over 20 years and I don't miss  
2 it. So I think there's some old drugs with some  
3 safety issues that we don't need to use anymore.  
4 We have newer drugs that don't have those safety  
5 issues. It's much more cost effective and  
6 beneficial to use the newer drugs.

7           And about clinical use of  
8 pharmacogenetics in practice, from what I heard  
9 today the most convincing argument was for  
10 clopidogrel, because if you come into the cath lab  
11 in acute coronary event you get a stent. They  
12 want to load you with an antiplatelet agent that's  
13 effective immediately. They can't wait for  
14 pharmacogenetic testing. So I would think, okay,  
15 why don't we use prasugrel, but that's an adult  
16 issue. If I'm a cardiologist I might could use  
17 clopidogrel, at least not initially. But that  
18 might be useful to get that testing, because maybe  
19 you'll want to switch them to that drug  
20 eventually.

21           In my practice we have a lab that's come  
22 by and they do some pharmacogenetic panel. I

1 don't know how good the lab is. I don't know how  
2 good the test results are. But they want to  
3 charge 300 bucks which doesn't seem too high for  
4 me. And they do this panel for ADHD drugs and  
5 psychiatric drugs, antidepressants, and the  
6 stimulants and atomoxetine, and can give you that  
7 information. Which I find interesting because if  
8 you can convince the insurance companies, which  
9 will take time, that you have data that show that  
10 it's cost effective. I mean one prescription for  
11 atomoxetine costs more than \$300 and so if you can  
12 show the insurance companies that you have good  
13 enough data to support what you do with  
14 pharmacogenetic testing, I think that's what you  
15 need to be able to use it. So you can avoid use  
16 of drugs that aren't going to be effective or  
17 aren't going to be tolerated.

18           And, last, as far as valproic acid, I  
19 really haven't had to use that in the at-risk  
20 population, but I think that's a situation where  
21 if I did have one of those patients and wanted to  
22 use the drug, I definitely want to do the testing

1 before I did use it. And I haven't looked at it  
2 recently, but when I've gone to epilepsy talks and  
3 talked to epilepsy challenges in my own practice, my  
4 understand is if you have a healthy child over the  
5 age of two who has epilepsy but otherwise normal  
6 neurologic examination and normal development,  
7 they don't have a risk of this liver toxicity.  
8 Now, adults do, because adults often have other  
9 issues that affect liver function, but I'm not  
10 aware of any case of fatal liver toxicity in a  
11 healthy child over the age of two.

12           So, again, that testing I think would be  
13 very helpful in children under two. And again  
14 today we have, you know, well over 15  
15 anticonvulsants we can pick from. And so when I  
16 started practice we had ethylene, phenobarbital,  
17 Tegretol, and depakote, and so it was a much more  
18 difficult choice back then. But now we have a lot  
19 of good choices of broad-spectrum drugs, and we  
20 can often avoid some of these safety issues.

21           DR. HUDAK: Michael?

22           DR. WHITE: Thank you. Michael White.

1 One of the things that were in the briefing  
2 materials and one of the areas that  
3 we've not discussed very much is the link between  
4 suspected problems with metabolism and  
5 pharmacogenetics and adequate testing. It strikes  
6 me that if this is going to work we have to have  
7 easily accessible, inexpensive testing available  
8 in the clinic when you're making your decisions  
9 about what drugs you're going to use and when  
10 you're going to start them, as you say, with a  
11 (inaudible) in the cath lab. You don't have time  
12 to send off and wait for the genetic test to come  
13 back to make your decision. With atomoxetine it  
14 seems like you could make your decision quickly  
15 and easily if you had adequate tests.

16 I remember when in the dark ages we used  
17 theophylline in the emergency room and suddenly we  
18 had a test that we could use in the emergency room  
19 for theophylline. It totally changed the way we  
20 approached things. And that's what we need to  
21 move toward.

22 The difficulty in doing that is no one's



1       been able to prove the financial link between the  
2       use of these tests and efficacy to this point to  
3       make it palatable to the insurance companies to  
4       cover it.  But I think, you know, if we can start  
5       with some fairly common drugs where we've got  
6       pretty good data, that there are significant  
7       differences in bioavailability -- can I use that  
8       word?  Is that appropriate instead  
9       pharmacokinetic/pharmacogenetic variability?

10                To say that we can get levels of  
11       atomoxetine that are useful or not, Dilantin or  
12       not, or drugs that are dangerous or not, they have  
13       to be easily available at the bedside, and I don't  
14       know how to encourage the devices, because these  
15       tests are -- that's the reason you were doing your  
16       presentation is that the testing that we do comes  
17       under device development and we encourage that.

18                And that rambles a lot.  Thank you.

19                MS. KELM:  Kellie Kelm, FDA.  I was just  
20       going to add that we've seen more rapid military  
21       testing being developed in the microbiology and  
22       virology fields.  It just seems to be where

1 obviously, you know, respiratory panels, flu  
2 panels -- you know, I think that's where they're  
3 getting reimbursement. And so you see a lot of  
4 the companies that are working on more rapid  
5 military tests are working on those types. I  
6 mean, there are companies working on it. I mean,  
7 obviously, FDA doesn't encourage it but, you know,  
8 other people can obviously try to encourage  
9 companies to take that same technology and think  
10 about developing it for other applications.

11 DR. HUDAK: Dr. Leeder, you referring to  
12 a chip from Michigan? And, I mean, I don't even  
13 know to begin to find that chip.

14 MR. LEEDER: Steve Leeder. What I was  
15 referring to was that for St. Jude, it is a group  
16 at the University of Wisconsin that does the  
17 genotype for them, and I believe that that lab  
18 uses the Affymetrix DMET chip.

19 But if I could just add one more comment  
20 related to that discussion, I'm not sure that the  
21 issue of rapid genotyping is going to be the  
22 answer. Rapid genotyping basically queries a

1 small number of relatively common genetic  
2 variance, and it is possible -- it's likely that  
3 that limited number of variances being tested is  
4 going to be widely applicable to a population.  
5 For example, for CYP2C9 in warfarin, the common  
6 variances that are tested are those that occur at  
7 a relatively high frequency in the Caucasian  
8 population and do not necessarily capture the  
9 variances that are going to be most relevant for  
10 an African-American population, for example.

11           The other issue is that for one of the  
12 studies that's come out of St. Jude looking at  
13 methotrexate pharmacokinetics and genetic  
14 variation in SLC01B1, a transporter that not only  
15 transports statins, it also transports  
16 methotrexate. It turns out that the burden of  
17 variability is not so much common variance in the  
18 SLC01B1 gene. It's a rare variance. And it's  
19 unlikely that you're going to capture those rare  
20 variances in just a limited genotyping platform.  
21 That's almost going to require a sequencing-based  
22 application.

1                   And, again, it boils down to precision  
2                   medicine and the individual patient. We want to  
3                   know what variances are present in the individual  
4                   patient as opposed to whether or not they have a  
5                   common variance.

6                   DR. WHITE: So, do you foresee the need  
7                   or the likelihood of developing whole genetic  
8                   sequencing anytime soon that would encompass all  
9                   the variance that one would need? I mean, it's  
10                  sort of: Do we start with small steps or do we  
11                  just go ahead and jump in and try to do  
12                  microarrays on everybody that cover every possible  
13                  sequence?

14                  MR. LEEDER: Steve Leeder. You know,  
15                  you can answer that question. I mean, I can think  
16                  of probably two or three different answers to that  
17                  question. You know, looking for common variance  
18                  is probably a reasonable place to start, and one  
19                  can do that if one accepts that they may or not  
20                  get a complete answer from a limited genotyping  
21                  chip.

22                  The other answer I would provide is

1       that, you know, maybe it's not so far in the  
2       future when organizations may decide that if a  
3       relatively inexpensive next-gen sequencing  
4       pharmacogenomic platform were available, it might  
5       be of advantage to that institution just to get  
6       the genetic information up front when a patient  
7       comes in the door, because you only have to do it  
8       once as long as you can get it into the system,  
9       which is a problem right now. Getting those  
10      results into an electronic health record is an  
11      issue right now. But once you get into the  
12      record, it's there. And then the only thing you  
13      have to worry about is making sure that the  
14      information travels with the patient if they go to  
15      another institution.

16                 You know, I mentioned that our  
17      institution is doing next-gen sequencing in the  
18      NICU. Well, within that whole genome is the  
19      pharmacogenome, and if we can cull the information  
20      that's going to be relevant, then it also exists.

21                 So, there are companies right now that  
22      are looking at targeted panels of maybe a hundred

1 genes, and some of the genes -- one of the common  
2 gene sets is one that is the very important genes  
3 that VIP set by the Pharmacogenomics Research  
4 Network -- PGRN. So, there are a couple of  
5 companies working on platforms of those. I think  
6 once you get the cost down below a hundred bucks  
7 or 50 bucks and you get to a capitated  
8 reimbursement for patients, maybe the economics  
9 might look a little bit more viable than they do  
10 right now. I don't know. We'll see what the  
11 future brings.

12 DR. HUDAK: So, I mean, just to amplify  
13 on the cost issue here, a couple of aspects of  
14 this are that if you send out a genetic test from  
15 a hospital, at least where I live, and the payer  
16 doesn't cover it, the hospital winds up footing  
17 the bill, whereas if you send it as an outpatient,  
18 then if the payer doesn't pay, it's the patient's  
19 responsibility. So, we doctors being fairly naïve  
20 about all of these details on finances may order a  
21 test and adversely financially impact either the  
22 hospital or our patients.

1                   There is a growing need for genetic  
2                   counselors, I think, in children's hospitals, and  
3                   one of the things that they do is they are very  
4                   expert in figuring out is this the best test for  
5                   this particular problem or not? Is it the most  
6                   efficient? Is it the cheapest?

7                   We have an endocrinologist who is very  
8                   high on imagining congenital hyperinsulinemia in  
9                   everybody, and it turns out that you can test for  
10                  this. One company it cost \$7,000; another company  
11                  it cost \$990. So, I think we've had three tests  
12                  sent all for \$990. They've all been negative,  
13                  thank goodness. But, still, it's another variable  
14                  in the equation for the medical system. Big  
15                  impact.

16                  Oh, I'm told Dr. Havens has a follow-up  
17                  question. Peter, are you there?

18                  DR. HAVENS: Yeah, but I'm afraid to  
19                  talk on the telephone now. Are you getting all  
20                  the defects, too, or is this okay?

21                  DR. HUDAK: I think you're okay. No  
22                  echoes.

1           DR. HAVENS: So, the issue of race has  
2           come up a couple of times, and we use the HOAB5701  
3           test to identify who is at high risk for abacavir  
4           hypersensitivity. The data were initially  
5           identified in a predominantly white population in  
6           Australia and applied across the board. So, now  
7           we're sending this test to decide if we can use  
8           the drug, which probably doesn't need to be sent  
9           in most African-Americans or people of African  
10          descent. So, to blindly apply these tests, which  
11          make their way into guidelines, may lead to  
12          inappropriately expensive testing when not really  
13          needed.

14                 The other issue -- and I particularly  
15          appreciate the neonatal example of Dr. Leeder --  
16          what happens when you have drugs with multiple  
17          clearance pathways where the predominant pathway  
18          might be faulty and delinquent but an alternate  
19          pathway might be able to increase its clearance?  
20          So, those kinds of situations, which happen when a  
21          lot of drugs infect us I think, mean that even if  
22          you've got a certain genotype the drug



1 concentration might be appropriate. So, from my  
2 perspective, we use a lot more drug concentration  
3 testing and a lot less genetic testing to define  
4 clearance.

5 DR. HUDAK: Dr. Wade and then Dr. Moore.

6 DR. WADE: Kelly Wade. I just would  
7 echo Dr. Haven's last comments that there are so  
8 many competing pathways.

9 I, too, really thought that was an  
10 excellent part of your presentation, Dr. Leeder,  
11 of neonatal pathways that may not have even turned  
12 on.

13 So, it feels like for pharmacogenetics  
14 to become a real-time practice to effect care at  
15 the bedside or in an outpatient clinic that it  
16 would be helpful to move forward also some easier,  
17 faster ways of therapeutic drug monitoring so that  
18 we would have the genetic information that would  
19 stand and we could use it across the years but  
20 that as we use that information to predict  
21 metabolic differences, hearing what I've heard  
22 today I think I would still want to know what a

1 level of that drug was for some confirmation that  
2 the patient really was a slow metabolizer or a  
3 fast metabolizer and to assess over the age range  
4 of pediatric development that perhaps a pathway  
5 has turned on or has not turned on.

6 So, I just feel very limited, I think,  
7 in evaluation of serious events or clinical care  
8 where I see patient differences that there really  
9 are very few drugs that we use that we have good  
10 therapeutic drug monitoring in.

11 DR. HUDAK: Let me -- before you answer  
12 -- you can ask that question, but that raises the  
13 issue of, you know, atomoxetine for instance. You  
14 know, rather than getting a pharmacogenomic test,  
15 the utility of being able to do the level of the  
16 drug seems to be as credible, in fact even more  
17 credible. You might want to comment on that on  
18 the relative cost of the tests.

19 MR. LEEDER: Steve Leeder. For that  
20 particular question first, I think the value of  
21 pharmacogenetic testing will be to anticipate  
22 what's going to happen. To measure the drug

1 concentration, the drug has to already have been  
2 administered. So, this is why we are trying to  
3 drift more toward building the models that would  
4 allow us to anticipate what a concentration time  
5 profile is going to look like given height,  
6 weight, age, and genotype. So, then that also  
7 requires that you have the pharmacogenetic  
8 information to input into the model, so it  
9 depends. If you have the genotype, good, and that  
10 would be the preferred scenario. Atomoxetine  
11 plasma concentration sampling is not routinely  
12 available, and most people would argue that you  
13 don't really need it, because atomoxetine is not a  
14 narrow therapeutic index drug.

15           But there's been a commentary written by  
16 Jose DeLeon that said that, you know, this  
17 shouldn't be -- pharmacogenetics shouldn't just be  
18 limited to narrow therapeutic index drugs,  
19 especially if you have a situation where exposures  
20 may not be adequate with existing guidelines. So,  
21 you're still back to that question. If you have  
22 the genetic information, that's good, you'd be

1       able to use it to do the therapeutic drug  
2       monitoring. Like I said, the dose has to be  
3       administered.

4                    But the comment I wanted to make to Dr.  
5       Wade was the fact that, you know, genotyping  
6       probably is not going to be all that helpful in an  
7       acutely ill newborn in the NICU setting just  
8       because everything is changing so quickly with the  
9       ontogeny. What we are starting to do now -- and I  
10      believe there are a number of different  
11      institutions that are starting to do opportunistic  
12      sampling -- is in the collected samples, not just  
13      to measure the disappearance with a parent  
14      compound but to also measure the metabolites so we  
15      know where it's going and so we know which  
16      pathways are changing the most during that  
17      critical period of illness and development and  
18      then use that information ultimately to help us  
19      out.

20                   DR. HUDAK: Thank you. Dr. Nelson.

21                   DR. NELSON: Yes, Steve, I guess a  
22      follow-up question for you. I mean, in terms of

1 the therapeutic drug monitoring, as one tries to  
2 develop a dataset that relates the changing  
3 pharmacogenomic -- I mean, not as the polymorphism  
4 -- I mean, I'd like to know if I've learned  
5 something. The polymorphisms will not change.  
6 The ontogeny will change.

7           So, you have this changing situation on  
8 top of an unchanging situation, but I guess I  
9 would assume that when you're trying to sort out  
10 that milieu, vis-à-vis a given drug, then in the  
11 research context you could still do, let's say,  
12 liquid chromatography against a reference sample  
13 to at least know what you're trying to predict. I  
14 mean, that sounds like a lot of the basic work  
15 needs to be done. I mean, that could be -- I  
16 mean, that they were doing that when I was a  
17 chemistry major a long, long time ago. So, I'm  
18 assuming that could be done in a research context.  
19 Is that correct?

20           MR. LEEDER: Yeah, it could, and I guess  
21 I'm drifting away from using the term "therapeutic  
22 drug monitoring," because a lot of people don't

1       like to do therapeutic drug monitoring, again, for  
2       the same issues of whether or not it's going to be  
3       reimbursed. I think it's useful to think of it in  
4       terms of exposure, checking the exposure to make  
5       sure that you know where you're at. We do that  
6       for aminoglycosides to make sure that the exposure  
7       is above the MIC, for example, and that  
8       concentrations are not sufficiently high that they  
9       raise the risk of nephrotoxicity or ototoxicity in  
10      the case of aminoglycosides.

11                 So, I think changing our frame of  
12      reference to make sure with any drugs that we're  
13      where we want to be makes sense. But that is only  
14      helpful if you know where you need to be, what  
15      exposure is associated with the desired response.  
16      And that's the dataset that's really missing. We  
17      don't get it from clinical trials.

18                 DR. HUDAK: Dr. Zuppa.

19                 DR. ZUPPA: Steve, so are you saying  
20      that if we had an idea of the genetic makeup for a  
21      gene responsible for metabolizing a certain drug  
22      and then we could a priori decide if the patient

1 was a fast, a slow, or a medium metabolizer, and  
2 then a priori decide on a dosing regimen, and then  
3 at steady state do some therapeutic drug  
4 monitoring to externally validate our genetic  
5 hypothesis about the disposition of that drug in  
6 the child?

7 MR. LEEDER: Sort of. So, let me try --  
8 take another crack at that.

9 Oh, for the record, Steve Leeder. So,  
10 the atomoxetine data that we generated in that  
11 pharmacogenetic, that genotype  
12 stratified PK study, we used the data, 200 and  
13 some data points, to build a population PK model, a  
14 population pharmacokinetic model. So, with that  
15 model we can then say, okay, for a given genotype  
16 -- you know, height, weight, age -- what dose  
17 would we need to give to get a P concentration of  
18 400 nanograms per ml? And so what we could -- so,  
19 that's what our prospectus study is doing right  
20 now. That's what we're shooting for. We're  
21 shooting for a P concentration of 400 nanograms  
22 per ml, and we're doing a full pharmacokinetic

1 curve because we want to see how well we predict  
2 the disposition profile. But ultimately what  
3 we're concerned about is how well did we do in  
4 hitting that target. So, in the future if we know  
5 where we need to be for a given drug target  
6 genotype, yes, I would suggest that's what we need  
7 to do once, you know, once we're at steady state  
8 to make sure that that's -- that we're where we  
9 want to be. But, you know, you have to have the  
10 data, and you can only do it basically one drug at  
11 a time.

12 But if I was going to toss out a  
13 rhetorical question, that would be that in a  
14 clinical trial when a participant in that clinical  
15 trial can be declared as a responder or a  
16 nonresponder, if we were to get a blood  
17 concentration that we could then start to get an  
18 idea of what exposure is associated with response,  
19 what exposure, range of exposures is associated  
20 with nonresponse, that you might start to be  
21 helpful information. Whether it goes into the  
22 label or not, you know, maybe the time is not yet



1 right. But it gives you some information to start  
2 to work with in our world at least.

3 DR. HUDAK: Okay, and to just finalize  
4 this session, the last aspect of this question, I  
5 suspect that I know the answer but we'll ask it  
6 anyway, and that is: If you did have this  
7 information, how would you go about interpreting  
8 it in your practice, or acting up on it? Is there  
9 a resource available to you now that can help you  
10 use this information if it were available?

11 I think I suspect probably not. So,  
12 that's fine. Okay, any other comments on this  
13 question before we move to the next, because it's  
14 been about an hour?

15 DR. HAVENS: Peter Havens.

16 DR. HUDAK: Peter. Go ahead.

17 DR. HAVENS: If I would just refer you  
18 to -- in response to your last question, I would  
19 refer you to the HIV guidelines, which do identify  
20 what to do when you get the pharmacogenetic test  
21 back. So, there are ways to codify and approach  
22 based on the genetic information, but as Dr.

1        Leeder points out, it's a lot of work, takes a lot  
2        of study, and it's a slow process. Also, in  
3        infectious diseases drug use, there's often a more  
4        clear pharmacokinetic/pharmacodynamic relationship  
5        that can be related to killing an organism, which  
6        makes it easy to see so that there can be an  
7        easier-to-establish relationship. But, yeah,  
8        there are guidelines for how to do that.

9                    DR. HUDAK: Okay, good point. All  
10        right, well, let's move on to the second  
11                    question then that we put up. I'll read  
12        it for the record. And this one says:

13                    "Please discuss the specific role of  
14        product labeling to inform your use of  
15        pharmacogenomic data in your clinical pediatric  
16        practice. Please address the location in the  
17        product label whether that should be as a box  
18        warning, a contraindication, warning of precaution  
19        or underdosage administration. As examples,  
20        please discuss the issues you would consider in  
21        deciding whether to order a poll test prior to  
22        prescribing valproic acid or a CYP2D6 test prior

1 to prescribing atomoxetine. Finally, please  
2 discuss how you would describe this testing to  
3 your patients and parents."

4 So, we'll start with that. I think this  
5 is a good question, because I think, having heard  
6 this discussion so far, I'm actually quite happy  
7 that FDA has not been very prescriptive about  
8 testing.

9 Ms. Moore.

10 MS. MOORE: I'm going to start at the  
11 end, because I don't have a lot of information  
12 about the first part.

13 I don't think we can overlook the  
14 ethical implications of having these conversations  
15 with patients and parents, especially in  
16 pediatrics, because if the recommendation is in  
17 conflict with what the patient or parent feels is  
18 the right thing to, the obligation of the provider  
19 is typically to the patient, not to the parent.  
20 And so it creates bit a bit of a conflict, but I  
21 just don't think you can always -- I think it's a  
22 little bit underappreciated.

1 DR. HUDAK: So, could you give a more  
2 concrete example of such a conflict?

3 MS. MOORE: I mean, I can in cystic  
4 fibrosis. Specifically, there are some  
5 gene-modifying drugs available now -- Ivacaftor  
6 and Lumacaftor -- that patients -- we have the  
7 data. We have the genetic data to show the impact  
8 of these medications for changing the function of  
9 the gene that regulates the sodium chloride in and  
10 out of the cell in cystic fibrosis, so we know  
11 that if these kids are put on these medications at  
12 a certain time, the impact on their life will be  
13 truly lifesaving.

14 It will change their life. It appears  
15 as if they don't have cystic fibrosis anymore.  
16 But a parent or a family member might not believe  
17 in medication, and so make a conscious decision to  
18 not go on that given medication. But the  
19 clinician's responsibility is to the patient, and  
20 we know that if the patient does not have that  
21 drug, the patient is going to continue to  
22 deteriorate and ultimately die because they didn't

1 have this medication.

2           Additionally, those drugs cost roughly  
3 \$300,000 a year per drug, and a lot of them are on  
4 a combination therapy. So, we don't have access  
5 to the medications. So, when the recommendation  
6 is being made, even if the patient wants to have  
7 access to it, they can't always get the  
8 medication.

9           And then additionally, on top of all of  
10 that, the endpoints that are being measured in  
11 the pharmacogenetics, there are patients who are  
12 benefitting from these medications being used off  
13 label, even though they don't meet the end points  
14 for indicated use.

15           So, on Ivacaftor, it might not change  
16 their sweat chloride level. However, it's helping  
17 them to gain weight, which is helping them to  
18 grow. It's declining the rate of exacerbation  
19 that they have. But when they're tested and the  
20 medication is not showing that it's changing the  
21 endpoint that's being measured, insurance is  
22 denying access to that medication. So, it's

1       tricky.

2                   DR. HUDAK: I think it was tricky for  
3       FDA to go through the approval process for the  
4       latter medication.

5                   Yes?

6                   DR. JONES: Bridgette Jones. Another  
7       thing I'd like to point out regarding discussing  
8       the results with parents and families and  
9       explaining to them the results -- usually we'll  
10      try to just discuss what the results mean for the  
11      specific drug they referred us to, but as you all  
12      know, these metabolizing enzymes metabolize  
13      numerous drugs. Then questions come up about:  
14      Well, if I have this genotype then how will it  
15      affect, you know, A, B, or C drug. And depending  
16      on how what other pathways are involved in those  
17      drugs and transporters and receptors, the answers  
18      may be different. So, it makes it even more  
19      complex. And so sometimes we'll ask families to  
20      contact us if they're going to use another drug  
21      that's metabolized by that same pathway. And we  
22      can provide as much information as we can, but I

1 would imagine that for practitioners, this would  
2 be a particularly difficult situation to navigate  
3 with families.

4 DR. HUDAK: Dr. Zupa.

5 DR. ZUPPA: I would second that. I  
6 think it's a slippery slope, because you go in and  
7 you start a discussion, and if you only have half  
8 the answers or a quarter of the answers, I think  
9 it can be not the best experience for the family  
10 and the patient.

11 DR. HUDAK: Maybe I can have the more  
12 specific question here. So we had discussions on  
13 four different drugs today with different language  
14 at different locations on the FDA label. Was  
15 there any one of these products that anybody  
16 thought might have been labeled differently or  
17 with different emphasis, perhaps at a different  
18 location than what had been provided on the label?  
19 That might be a concrete point of discussion if  
20 someone has a thought about that.

21 Dr. Wade.

22 DR. WADE: Just a comment that it's such

1 an exploratory field right now, that a lot of the  
2 information in the label obviously came in  
3 different sections if it had to do with laboratory  
4 monitoring or a side effect or dosing. And I'm  
5 just wondering, assuming that this field expands,  
6 if I had thought, oh, I think there are some  
7 pharmacogenetics associated with this drug,  
8 there's not a consistent place in the label to  
9 look for that. And one theme that has come out of  
10 this is that in the clinical practice, not  
11 everyone is well versed in pharmacogenetics, and  
12 so it may be just that we have an inkling, and I  
13 just wonder if this field expands if it would be  
14 worth having a consistent location in the label  
15 rather than having to know where the  
16 pharmacogenetics effects, drug disposition or drug  
17 toxicity is and then having to look in a specific  
18 section. I'm sure there are pros and cons of  
19 that.

20 DR. HUDAK: Dr. Nelson.

21 DR. NELSON: I'm not going to comment on  
22 that directly, but let me make an observation in



1       pediatrics and then see if Mike has some thoughts  
2       on that.

3                       In pediatrics, for example, you know,  
4       pediatric studies done under BPCA and PREA that  
5       you see here in terms of the post-marketing  
6       Pediatric Focus Safety Review, if the drug does  
7       not get the indication then in Section 8.4 I think  
8       it is -- or is it -- yeah, 8.4, you'll see a  
9       description of all the pediatric information  
10      there. But if it gets the indication, the data  
11      will be dispersed in whatever area of the label it  
12      should be, whether it's indication, dosing,  
13      safety. Because they've gotten the indication,  
14      the assumption is you'll look at the whole label.  
15      Maybe that's incorrect, but the assumption is that  
16      one will look for that data.

17                      Now whether that's an appropriate model  
18      for pharmacogenomics or not I think is an open  
19      question. And certainly since this is closely  
20      related to clinical pharmacology, there is a  
21      clinical pharmacology section. So, I'm not sure  
22      what the thinking is. I honestly don't know what

1 the thinking is in terms of where that was  
2 dispersed in labeling or whether it's similar or  
3 different from the pediatric thinking.

4 DR. HUDAK: Mike Pacanowski?

5 DR. HAUSMAN: Yeah, I'll just --

6 DR. HUDAK: Oh, I'm sorry, go ahead.

7 You're first and then Dr. Hausman.

8 MR. PACANOWSKI: Sure, just to build on  
9 what Skip had said. If there are specific dosing  
10 instructions, that will typically fall under  
11 dosage administration, or if it's a clear untoward  
12 effect, it'll end up in contraindications or some  
13 other more permanent area of labeling. There is a  
14 section, a subsection, of clinical pharmacology  
15 where data and more transparent presentation of  
16 information is often presented. We typically  
17 don't put the dosage or usage instructions down  
18 there, because it's buried in the label. But it  
19 cross-references with other sections of labeling.

20 DR. HAUSMAN: Hi, Ethan Hausman. I was  
21 going to say basically the same thing, but I would  
22 add on that for failed studies when the

1 information is limited to Section 8.4, what we  
2 generally include there is a description of the  
3 study, but we try to avoid any appearance of  
4 implying an indication.

5           So, in that scenario, we might not even  
6 provide comprehensive safety information if it has  
7 been similar to studies in other populations, like  
8 adults. It might be distilled to a simple  
9 sentence that safety and effect -- safety was  
10 similar.

11           In the scenario which we don't imply  
12 frequently but we do occasionally, if there is a  
13 new safety signal in the pediatric study that  
14 failed, we will describe that in Section 8.4. So,  
15 one might supposed that in a failed study if data  
16 were good, if there was an adequately performed  
17 study, and it just happened to not show  
18 effectiveness, if the data were actually  
19 acceptable I could envision a possibility where  
20 some pharmacogenomic/pharmacogenetic data might  
21 make it into 8.4. But generally if the study has  
22 failed, we keep that description very, very brief.

1 DR. HUDAK: Dr. Turer and then Dr.  
2 Kaskel.

3 DR. TURER: So, as a primary care  
4 physician, I think that a lot of this is not used  
5 in pediatric primary care. Because I'm also a  
6 practicing internist, I think in internal medicine  
7 we've learned a lot of lessons about many of these  
8 interactions, which may provide some insights.

9 So, for example, with warfarin, when we  
10 looked at the benefit of doing the genetic testing  
11 in well-conducted studies, it didn't really impact  
12 clinical care.

13 In contrast, I think the data were very  
14 compelling for efavirenz. I think that's a great  
15 example of, you know, they did the trials; they  
16 showed that that made an impact. And I think that  
17 it partly has to do with the severity of the  
18 adverse effect that you're trying to prevent --  
19 the ability to predict the response based on  
20 whatever the, you know, the genetic mutation is,  
21 and then the availability of alternative therapy.

22 And for that final one, I think Plavix

1 is actually a very interesting case in point,  
2 because we administered in these very acute  
3 situations, and for a very long time it's the only  
4 one that we did administrative in the cath lab.  
5 And so then there were a number of studies looking  
6 at these genetic interactions. But by the time  
7 they came out, then we had a whole host of  
8 alternative drugs. So, now it's kind of a moot  
9 point in terms of Plavix.

10 So, I think, you know, thinking really  
11 smartly about what are the drugs that have been in  
12 use for a very long time that we could really be  
13 helped by in primary care and throughout out, I  
14 echo -- I think steroids are one of them.

15 And then the final thing -- so, things  
16 are in practice for a long time that are not going  
17 to time out -- the final thing, I think our  
18 patients read the labels. Physicians don't. And  
19 I am struck by the number of patients that come to  
20 me after I've prescribed a drug and say: You  
21 know, I was going through the label with the  
22 pharmacist, and it says X, Y, and Z.

1                   So, I think it's very important to get  
2           -- you know, we have a lot of physicians on the  
3           panel but also the patients, and how to -- if that  
4           information is in the label, how do we pull the  
5           patient into this conversation? And until we do  
6           that, I don't know that -- you know, I would  
7           submit that we're not ready to put it in there  
8           unless we have fantastic data like the efavirenz.  
9           We have a drug that is not going to time out. A  
10          clear response, the ability to predict response,  
11          and a way to communicate with patients about it in  
12          a way that makes sense.

13                   DR. HUDAK: So, Dr. Kaskel is first and  
14          then --

15                   DR. KASKEL: Recently I learned about a  
16          special population of children who may need to be  
17          treated with allopurinol, and it was a response to  
18          an NIH RFA for treatment of children with chronic  
19          kidney disease. And we submitted an application,  
20          and someone brought up on the call that  
21          allopurinol has a risk factor. If you're of Asian  
22          descent you can develop a very, very severe

1 cutaneous reaction. Very severe. And it's  
2 associated with HLAB5801 allele.

3           It was news to me. We don't use  
4 allopurinol all that much, but this NIH study is  
5 trying to address treatment of uric acid  
6 abnormalities in children who seek AD, because it  
7 hasn't been studied. So, it turns out that the  
8 FDA label does not discuss this risk. No one knew  
9 this except one person on the call who said:  
10 You'd better look into this and put in your  
11 application that you're going to screen every  
12 subject in the study, if you're granted, for this  
13 allele.

14           It is listed in the CPIC. It recommends  
15 testing before treatment. So, here's an  
16 opportunity with a drug that's been around for a  
17 long time, not used for gout in children very  
18 often but now is being promoted to be used to  
19 prevent cardiovascular disease in children with  
20 CKD -- mild to moderate CKD. And the information  
21 isn't there. And what I would envision at some  
22 point, when we go into our EMR and we prescribe

1       that drug and the EMR has the ethnicities in it  
2       already, up comes a little tab that says: Hello,  
3       you need to test for this. And I certainly  
4       wouldn't have known this nor told the parent that  
5       we need to test for this. Just an example.

6                 DR. PORTMAN: This is Ron Portman. I  
7       like Steve's vision of the future, and I just want  
8       to say that I think that in 10 years this  
9       discussion will be very different. I think that  
10      most large pharma at least have departments of  
11      precision medicine, and much of what we're doing  
12      in developing new drugs is considering the  
13      concepts of precision medicine rather than taking  
14      a drug that only 50 percent of patients responded  
15      to and just saying: Well, that doesn't work out.  
16      Now the question is: Why did only 50 percent  
17      respond and begin to explore some of these  
18      pharmacogenetic issues? And I think that the idea  
19      that we were seeing cancer with codiagnostics is  
20      going to be present in many drugs in the future.

21                DR. HUDAK: So, I think we have, as  
22      usual, a robust spread of thoughts on this



1 particular issue, and I can see both points of  
2 view as to too much or too little information on  
3 this. I tend to air on the -- maybe, too much  
4 information, because it is information that can be  
5 hopefully dealt with. But that's a good point  
6 about the allopurinol.

7           You know, it's interesting the  
8 approaches that pharmacies have across the country  
9 to this. You know, St. Jude's, I referred to  
10 before, has this program, and their approach to  
11 the codeine issue was they tested all of their --  
12 you know, not all of their -- 80-something percent  
13 I think of their sickle cell patients, who are the  
14 bulk of the patients who were prescribed codeine,  
15 were tested. And the pharmacy systems came up  
16 with alerts. I mean, it said: If this patient is  
17 an ultra-rapid metabolizer, don't give the drug;  
18 here are some alternatives. You know, they had 20  
19 percent where there was no information and the  
20 physician was warned, you know, no information,  
21 don't know. And so they had a very good -- this  
22 has worked very well. They had, really, only one

1 case in which a possibly at-risk patient was  
2 treated with codeine, and that turned out to be by  
3 physician discretion, because that patient had  
4 received codeine before and had no, you know, no  
5 issues.

6 Other hospitals, like Boston Children's  
7 Hospital, they dealt with the codeine problem by  
8 just removing it from the formulary, because there  
9 are other drugs that are as safe and effective --  
10 as effective and more safe or safer. So, there's  
11 a huge variation, I think, in practice on this.

12 DR. HUDAK: Any other comments? Dr.  
13 Havens? Dr. Kishnani, anything else?

14 DR. HAVENS: Thank you. It's been a  
15 rich discussion. I appreciate it.

16 DR. KISHNANI: This is Pryia. I have a  
17 comment.

18 DR. HUDAK: Go ahead.

19 DR. KISHNANI: Mike, I'm glad that the  
20 topic of allopurinol came up. It almost became  
21 medical legal at our university at one point, and  
22 so one of my questions and concerns is that this

1 is definitely an evolving field and, yes, we must  
2 have it on the label, but it must be in a place,  
3 you know, where it's easily available or seen.  
4 But, on the other hand, it also gives leverage  
5 from an insurance company reimbursement  
6 perspective, because I think otherwise we end up  
7 opening ourselves up, that if we prescribe certain  
8 medications which end up with a complication and  
9 if it's not in an identified spot in the label, we  
10 could get in trouble. So, I do believe that we  
11 have to do these things, but it has to be done in  
12 a systematic way so that, you know, as physicians  
13 not only are we equipped but we are also covered.

14 DR. HUDAK: Yes, thank you for that.

15 DR. HAVENS: Peter Havens.

16 DR. HUDAK: Yes, Peter.

17 DR. HAVENS: For abacavir, the HLA  
18 association with hypersensitivity is in a boxed  
19 warning. So, it's very clear. But, as we talked  
20 about with abacavir, that's mostly for whites.  
21 Here you're making a pharmacogenomic requirement  
22 that mostly applies to Han Chinese. And so it

1 shows the complexity of trying to do this. You  
2 would argue, consistent with the abacavir, that  
3 you'd want it in a boxed warning. But then are  
4 you going to apply it to everybody, or are you  
5 going to only apply it to Han Chinese, the  
6 population within which it's been found to be an  
7 issue?

8 DR. HUDAK: Excellent question. I have  
9 the question for Dr. Nelson, so the first  
10 question is: Your impression of the  
11 field in terms of the rapidity with which  
12 information is being generated now, the  
13 anticipation of the trajectory of this in the  
14 future, and what mechanisms FDA might be able to  
15 have should you decide to be more generous in  
16 providing this information in label form. You  
17 know, with some journals, like Pediatrics, they do  
18 not allow in certain articles publication in print  
19 of tables or whatever with information that can  
20 change rapidly. So, their policy is basically to  
21 put a URL in there, that you can click on the URL  
22 and it'll provide you with up-to-date information

1       because it may change every couple of months,  
2       rather than memorizing something that's going to  
3       be out of date by the time the journal comes to  
4       press. So, I don't know to what extent that sort  
5       of approach might be something that would meld  
6       with this rapidly expanding field in the future.  
7       For you, just some comments.

8                     DR. NELSON: So, let me just give some  
9       thoughts about what I've heard, and this is just  
10      what I've heard, not necessarily what FDA has  
11      heard, and I'm not sure what it means to say what  
12      FDA hears or not, frankly.

13                    You know, there's I think a promise of  
14      pharmacogenomics that everybody recognizes to the  
15      extent to which precision medicine could ideally  
16      offer improved efficacy and decreased adverse drug  
17      effects. If you get the right exposure and don't  
18      necessarily end up with the variability that we  
19      get by just picking dose, and I heard -- and I  
20      certainly heard the theme of what drugs would we  
21      love to have these data on would be those that we  
22      see this great variability in response, whether

1       it's corticosteroids or others, that it's not that  
2       we necessarily have those data now, but could we  
3       understand that variability better.

4               Now, I doubt we would eliminate all  
5       variability by getting these data, but that would  
6       be something to be gained. I find it challenging  
7       to think about what I think Steve challenged us to  
8       think about is -- you know, when we think about  
9       phase 1, early phase trials is to get the dose  
10      right. What he's really saying is maybe we should  
11      start thinking about getting the exposure right  
12      and maybe that's going to require pharmacogenomic  
13      thinking to be able to get the exposure right.

14              But how that gets incorporated into  
15      study designs at this point I think is a complex  
16      question. I mean, he offered some suggestions for  
17      pharmacogenomic stratification, if you will, of  
18      early PK testing, but I think, you know, I would  
19      have to sort of take that back and think about  
20      that with people who have thought about that a  
21      fair amount. But optimizing exposure I think is  
22      what we're all about in thinking about the right

1 dose to the right child at the right time.

2           What makes that more complex, you know,  
3 so we would think of exposure ranging instead of  
4 dose ranging. We often think of dose ranging as  
5 what we have to do in a trial boon. What makes  
6 that complex, then, is pulled into the autogeny of  
7 the target -- and to the extent that might be  
8 changing. So, you not only have -- you know,  
9 you're changing how much you're putting into the  
10 organism, but you're also changing what you're  
11 trying to hit at the same time, and that may be  
12 more of an issue for infants and younger children.  
13 It may not -- I don't know. It depends on the  
14 disease; it depends on the drug.

15           So, I've certainly heard that there are  
16 substantive differences when you look at the  
17 different drugs, when you look at the different  
18 metabolic pathways. Are there alternate pathways?  
19 You're looking at the disease. You're looking at  
20 the population. You're looking at genetics of  
21 that population. It's clear that one size is not  
22 going to fit all in this area. And I agree with

1 Ron that this is going to be a moving target, you  
2 know, as the cost of the ability to do these tests  
3 comes down.

4 I won't mention the company, but for a  
5 present I was given my -- I sent my DNA and got it  
6 back last week, you know, heritage and things, and  
7 I'm pleased to say I'm not at risk for early  
8 Alzheimer's. But I knew that was my family  
9 history anyway, so it wasn't -- it didn't add a  
10 whole lot. But, you know, you can get all of  
11 this, and I was able to download my genome and  
12 then upload it into heritage.com. Well, oops,  
13 sorry, don't have any stock in that either.  
14 (Laughter) But anyway, to do that was sort of  
15 fun, you know, and that was \$250. So, I'm  
16 assuming that this technology will be coming down  
17 in price, and the point at which you're able to  
18 show that you save money by improving efficacy and  
19 degaussing adverse events, I would be interested  
20 if the institutions that are starting to do what  
21 Steve says Children's Mercy is thinking about --  
22 predisposition or, you know, not just forensic



1 testing but prior testing -- to show that within  
2 that system costs have been -- I'm assuming then  
3 that would begin to get to the point where it  
4 would compel people to do it, not only in clinical  
5 decision-making but in the cost effects.

6           So, from my point of view, I think the  
7 challenge for FDA is, you know, we're not into  
8 costs -- that's not our remit -- but the question  
9 is: How can we incorporate some of this thinking  
10 into prospective study design? You heard from  
11 Mike's presentation often that comes in sort of in  
12 the post-approval phase. But how much of that can  
13 be done up front? How much do you know up front?  
14 You may not even know it until you begin to see  
15 that variability.

16           I could go on, but those are some of the  
17 themes that I heard in terms of the complexity of  
18 this area. And, frankly, I think part of the  
19 intent of not -- when we got into the discussion  
20 of favorance at the previous meeting was to imply,  
21 yeah, this is more a complicated area than just  
22 saying: Well, we ought to throw something into

1 the label. So, I think we showed that.  
2 (Laughter) I think we demonstrated that. It's a  
3 lot of information, so it's -- but, you know, I  
4 think everybody, at least from the FDA, may have  
5 taken different themes aside: We'll take it back,  
6 we'll think about it. But, you know, there wasn't  
7 any real deliverable here in terms of what we were  
8 thinking we would do to change our practice. That  
9 was not the intent, it was to have a discussion  
10 that would hopefully both inform you and inform us  
11 about the complexity of this area. So, I think  
12 we've achieved that at the very least.

13 So -- I know, welcome to entertain any  
14 other comments, but those are my thoughts --  
15 again, just my personal thoughts -- listening to  
16 the conversation.

17 DR. HUDAK: Dr. Wade?

18 DR. WADE: Skip, can you -- Kelly Wade  
19 -- can you comment on what was raised about  
20 allopurinol, because it struck me as well that  
21 pharmacogenetics changes over time and how we use  
22 it and who's its advise. But labels don't change

1 in real time. You know, they're not as easily  
2 updated. So, what resonated with you in that  
3 allopurinol discussion?

4 DR. NELSON: Well, so, labels are a  
5 complex area, but if there is something that  
6 requires a labeling change based on safety, FDA  
7 has the authority to do that. I don't know enough  
8 about that. I mean, I guess the question would be  
9 the extent to which that information tracks  
10 phenotype -- in other words, should that --  
11 Peter's comment I thought was very interesting,  
12 and I didn't know that about abacavir. It's in  
13 there as a warning, and so everybody gets tested  
14 even though it was developed in Australia and it's  
15 applied to African- American heritage and so on  
16 and so forth. So, is that going to be the same  
17 issue with allopurinol if it's found in this  
18 population? But then we put it somewhere and then  
19 everybody gets tested.

20 I don't know the answer to that  
21 question. I think it's an interesting set of  
22 issues. But I would hesitate to say anything

1 other than, you know, I think it's worth thinking  
2 about, but if FDA concluded we should change a  
3 label for safety reasons, I know we have the  
4 authority to do that, but whether that's the right  
5 thing to do or not, in that case, I would not  
6 comment on.

7 DR. HUDAK: Dr. Sayej?

8 DR. SAYEJ: I would just like to make  
9 one final comment. If the FDA decides on making  
10 sure that all -- well, everyone's goal is to make  
11 sure that the patient and the prescribers are well  
12 informed of every detail about the medication that  
13 they're prescribing or taking and making sure that  
14 the patients are safe. So, providing this  
15 information in the label is very important. So,  
16 if there's a drug that has a test that can  
17 potentially prevent adverse events or further  
18 complications, then that's great. We need to have  
19 that test available, and we need to be able to  
20 order that test.

21 Unfortunately, that's not always the  
22 case. These tests are not always commercially

1 available, and doctors struggle to figure out  
2 where to send these tests or how to get them  
3 covered and how to monitor or the tests for  
4 monitoring are not covered. And so if we -- I  
5 think we have to take into consideration all of  
6 these aspects and not just, you know, what is the  
7 label going to say: Well, what are the  
8 implications on clinical practice? What are the  
9 implications on cost to the patient? What are the  
10 implications on the physician's practice? You  
11 still don't want to throw the physicians under the  
12 bus by saying: Oh, well, this isn't labeled; you  
13 need to check this before you start the patient on  
14 the medication.

15 We all know that we prescribe  
16 medications all the time off label, and physicians  
17 do that every single day in their practice. So,  
18 what I'm trying to say is we need to take all  
19 these things into consideration and really kind of  
20 make sure that if we enforce something like this,  
21 we have the resources where patients and  
22 physicians can follow through with this

1 medication.

2 DR. HUDAK: Dr. Callahan.

3 DR. CALLAHAN: Yeah, I just want to make  
4 a comment about the carcinogenic testing.

5 So, I work in an outpatient setting in  
6 an outpatient practice. I'm not tied to a  
7 hospital, and I no longer order my genetic testing  
8 through Washington University, because they don't  
9 want to do the work to get it covered, and our  
10 genetics department is the same.

11 But if you're not in an institution,  
12 it's very easy to get good genetic testing through  
13 many labs. I can get you the names if you want  
14 them. And you send them the information. You  
15 send them the requisition. You send them the  
16 insurance. You send them the diagnosis. And they  
17 won't require your staff to do it. They'll do the  
18 work. They'll get it covered. Or they'll do it  
19 for a hundred dollars just to do it, because they  
20 want to provide genetic testing. But I think when  
21 you're with institutions they're going to charge  
22 the institutions as much as they can get out of



1 think if you look back Mike Pacanowski's slides,  
2 he talked a lot about the uncertainty, about the  
3 place of this testing, and the context of the  
4 clinical decision-making, and so I think we're  
5 certainly in agreement that the decision to put  
6 something on the label has to take into account  
7 the factors that you outlined in terms of the  
8 complexity, the physician decision-making, and so  
9 on and so forth.

10 And I will say, anybody who wants  
11 information about that kind of testing, I suggest  
12 you do it after the meeting. You can certainly  
13 check with Dr. Callahan about the availability of  
14 that testing since the FDA shouldn't be a part of  
15 that exchange.

16 DR. HUDAK: It does bear a comment,  
17 because it is part of our daily lives, and  
18 specialists don't have to deal with some of the  
19 implications of all of this. Primary care  
20 physicians often times do because of the  
21 attribution of cost -- the primary care provider  
22 that may determine, you know, how well they do.



1 It's a real issue, yeah.

2 DR. NELSON: All right, Skip Nelson  
3 again. Who we knew it was, which is why on the  
4 first question we alluded to please talk about the  
5 challenges. So, we were not blind to the fact  
6 that there are those challenges. All I'm  
7 suggesting is if you want specific advice about  
8 the company to contact, I suggest you do that  
9 after the meeting is over, over dinner or  
10 whatever.

11 DR. HUDAK: All right, any other  
12 thoughts? If not, I think on behalf of the  
13 committee, we want to thank Dr. Nelson for  
14 organizing this program and the excellent speakers  
15 from FDA and Dr. Leeder from Missouri who educated  
16 and enthralled us with a lot of information today,  
17 and even though we haven't come to definite  
18 conclusions, it certainly informs us going  
19 forward. So, thanks.

20 (Whereupon, at 4:59 p.m.,

21 PROCEEDINGS were adjourned)

22 \* \* \* \* \*

## 1 CERTIFICATE OF NOTARY PUBLIC

## 2 COMMONWEALTH OF VIRGINIA

3 I, Carleton J. Anderson, III, notary  
4 public in and for the Commonwealth of Virginia, do  
5 hereby certify that the forgoing PROCEEDING was  
6 duly recorded and thereafter reduced to print under  
7 my direction; that the witnesses were sworn to tell  
8 the truth under penalty of perjury; that said  
9 transcript is a true record of the testimony given  
10 by witnesses; that I am neither counsel for,  
11 related to, nor employed by any of the parties to  
12 the action in which this proceeding was called;  
13 and, furthermore, that I am not a relative or  
14 employee of any attorney or counsel employed by the  
15 parties hereto, nor financially or otherwise  
16 interested in the outcome of this action.

17

18 (Signature and Seal on File)

19 Notary Public, in and for the Commonwealth of  
20 Virginia

21 My Commission Expires: November 30, 2020

22 Notary Public Number 351998

