UNITED STATES FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Monday, March 6, 2017

PARTICIPANTS:

Welcome and Introductory Remarks:

MARK HUDAK, MD
Chair of Pediatric Advisory Committee (PAC)
Assistant Dean of Managed Care for the
University of Florida College of Medicine - Jacksonville
Assistant Medical Director
Neonatal Intensive Care Unit
University of Florida Health Science Center
Jacksonville, Florida

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

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

Opening Statement:

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

Pediatric Focused Safety Review Update - Exjade (deferasirox):

PETER WALDRON, MD
Division of Pharmacovigilance II
Office of Pharmacovigilance and Epidemiology
Center for Drug Evaluations and Research (CDER), FDA

PARTICIPANTS (CONT'D):

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

Standard Review of Adverse Event Presentation Kuvan (sapropteria dihydrochloride):

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

Nitropress (sodium nitroprusside):

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

The Role of Pharmacogenomic Data in Pediatric Therapeutics:

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

Pharmacogenomics in Pediatric Product Development and Labeling:

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

PARTICIPANTS (CONT'D):

Case Studies in Pharmacogenomics:

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

Analytical and Clinical Validation of Pharmacogenetic Tests:

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

Clinical Implementation of Precision Therapeutics In Children:

J. STEVEN LEEDER, PharmaD, PhD
Director, Division of Clinical Pharmacology,
Toxicology and Therapeutic Innovation
Associate Chair-Research
Department of Pediatrics Deputy Director
Children's Research Institute
Children's Mercy Kansas City
Professor of Pediatrics and Pharmacology
UMK Schools of Medicine and Pharmacy

Discussion:

MARK HUDAK, MD
Chair of Pediatric Advisory Committee

Summary and Wrap-up:

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

PARTICIPANTS (CONT'D):

Adjournment:

MARK HUDAK, MD
Chair of Pediatric Advisory Committee

* * * * *

P R O C E E D I N G S

(8:30 a.m.)

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

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

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

Academic General Pediatric Scholarship Program.

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

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

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

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

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

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

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

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

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

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

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

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

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

Office of Pediatric Therapeutics at FDA.

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

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

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

MS. WEINEL: Hello.

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

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

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

DR. HAVENS: I'm Peter Havens. Pediatrician (inaudible) Infectious Diseases at the Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee. And there's a lot of feedback on my phone. I don't know what's going on.

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

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

DR. HUDAK: Yes.

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

DR. KISHNANI: Yes. Yes.

MS. WEINEL: Great.

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

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

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

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

DR. MCCUNE: Hello.

DR. NELSON: (Laughter)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

statement? Okay. Well then --. Hmm?

MS. BRILL: They cancelled last (inaudible).

DR. HUDAK: They cancelled?

MS. BRILL: Yes.

DR. HUDAK: So we will --

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

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

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

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

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

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

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

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

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

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

The FAERS analysis. The Safety

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

the upper limit of normal, after continuation or interruption of deferasirox therapy in the subset of events, where the ALT, alanine aminotransferase, was within normal limits prior to the adverse event. Overall, 17 percent of 157 adverse events in 107 unique pediatric patients with fever, were followed by some evidence of liver injury. Transaminases were elevated after 13 percent of fever events, when the study drug was adjusted. Or -- and

percent when it was not. This table shows the proportion of dehydration adverse events with transaminase elevations above the upper limit of normal, after continuation or interruption of deferasirox therapy in the subset of events where the ALT was within normal limits prior to the adverse event. Overall,

percent of 91 adverse events in 73 unique pediatric patients with signs or symptoms of dehydration, were followed by some evidence of liver injury. The proportion of events with transaminase elevations appears similar whether a

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

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

current labeling for deferasirox mentions dose adjustment or interruption.

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

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

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

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

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

warning for hepatic toxicity, renal toxicity and in the guidelines for monthly, and in some cases, more frequent laboratory monitoring. The analysis of study, CICL670A0107, showed the following fever or dehydration events subjects frequently had, sorry, the following fever or dehydration events subjects frequently had, lab values for creatinine or urine protein to creatinine ratio, which were in the range that the current deferasirox label uses to indicate dose reduction or interruption treatment. FDA has received case reports of serious and fatal liver and kidney failure in young children, taking deferasirox, including the index case. Several with elevated ammonia levels and -- and they have been described. Or, they have been described in those reports. And so we continue to probe whether predictors of toxicity can be better characterized and mitigated, especially in young children. This slide summarizes our continuing efforts on this -- on this concern. For hyperammonemia, we are evaluating 14 cases from FAERS. These cases

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

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

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

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

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

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

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

DR. HUDAK: And just to close the issue

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

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

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

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

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

DR. CREW: Page Crew, Safety Evaluator,

Division of Pharmacovigilance II.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. HUDAK: Dr. White.

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

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

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

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

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

lower iron burden are at higher risk for problems.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

even in there. It's almost misleading.

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

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

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

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

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

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

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

DR. HUDAK: Dr. White.

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

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

DR. HUDAK: Dr. Cnaan.

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

DR. GELPERIN: Yes.

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

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

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

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

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

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

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

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

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

DR. HUDAK: Dr. Turer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. WALDRON: Oh I see. Generic AKI.

DR. KASKEL: Right

DR. WALDRON: Okay good. Thank you.

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

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

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

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

DR. HUDAK: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. KISHNANI: I see.

DR. HUDAK: I don't see any further

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

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

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

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

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

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

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

DR. Spauldingthe DPMH presenter is here. The

DPMH presenter is here for Kuvan.

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

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

MS. WEINEL: Yeah.

DR. NELSON: The answer is yes.

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

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

DR. SPAULDING: Yes.

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

DR. SPAULDING: Sure.

DR. HUDAK: -- to the group?

DR. SPAULDING: Thank you.

DR. HUDAK: Thank you.

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

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

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

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

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

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

outcome of death. There were four reported death cases. The age range for these patients was 10 months to 7 years. Two fatal cases contained insufficient clinical information. In the third death case a

year-old male with a history of atypical PKU and seizures died in the middle of the night after having a seizure. He had profound motor and cognitive disease and had been on Kuvan for three years at the time of his death. The seizure and death were contributed to his underlying medical condition. The remaining death case involved a 15 month-old female with a history of atypical PKU who had been receiving Kuvan 600 milligrams orally once daily for approximately 1 month when she experienced apneic events after receiving a dose of Kuvan. Concomitant meds included baclofen, gabapentin, bromide and Carbidopa/levodopa and glycopyrronium. The event was reported as severe and the patient died two days after the report apneic events. Of note the patient did have a DNR status. We reviewed 43 reports that described

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

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

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

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

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

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

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

DR. SWANK: Safety Evaluator, Division of Pharmacovigilance.

DR. GREENE: Patty Greene, drug utilization.

DR. SMPOKOU: Patroulas Smpokou, clinical reviewer, Division of Gastroenterology and Inborn Error Products.

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

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

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

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

DR. HAUSMAN: Okay.

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

think you mentioned there was a decrease?

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

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

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

DR. LEVIN: Right.

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

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

DR. HUDAK: Dr. Callahan.

DR. CALLAHAN: Just a follow-up. I

think in the 7 year-old boy they describe what was likely SUDEP up or Sudden Unexplained Death in Epileptic patients and some of those patients it may be a cardiac arrhythmia that triggers a seizure and a death. So I'd be interested if we had any EKG data on the patient prior to the child dying and even for the

month-old female also -- again, any EKG baseline.

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

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

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

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

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

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

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

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

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

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

say.

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

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

DR. HUDAK: Dr. Cnaan.

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

DR. HUDAK: Dr. Nelson.

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

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

DR. LEVIN: Sure.

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

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

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

DR. HUDAK: Dr. Hausman .

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

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

UNIDENTIFIED SPEAKER: Now, you can go around.

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

DR. HAVENS: Approve. Havens.

DR. KISHNANI: This is Priya. Approve.

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

DR. TURER: I approve.

DR. SAYEJ: Wael Sayej. I approve.

DR. KASKEL: I approve. Rick Kaskel.

DR. ANNE: Premchand Anne. I approve.

DR. WADE: Kelly Wade. I approve.

DR. CATALETTO: Mary Cataletto. I approve.

DR. MOORE: Erin Moore. I approve.

DR. WHITE: Michael White. Agree.

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

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

DR. CNAGN: Avital Cnaan. I approve.

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

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

(Recess)

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

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

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

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

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

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

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

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

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

DR. MULUGETA: Lily Mulugeta.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. MULUGETA: Slide 12, please.

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

case that was discussed.

DR. MULUGETA: I can also comment.

DR. HAUSMAN: Yeah.

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

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

DR. HUDAK: Dr. Anne.

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

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

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

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

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

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

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

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

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

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

DR. HUDAK: Okay --

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

DR. HUDAK: Yes.

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

clinical pharmacologist and toxicologist review was in adults.

DR. WHITE: Yes.

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

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

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

DR. HUDAK: Dr. Nelson.

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

DR. WHITE: I'm sorry.

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

DR. WHITE: I can't read that.

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

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

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

DR. HUDAK: Dr. Havens.

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

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

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

UNIDENTIFIED SPEAKER: Can you identify yourself?

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

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

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

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

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

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

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

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

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

DR. CHEN: Yes.

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

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

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

UNIDENTIFIED SPEAKER: Please identify yourself.

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

DR. HUDAK: Dr. Cnaan.

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

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

DR. DWIVEDI: That's correct.

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

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

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

DR. HUDAK: Doctor.

DR. HAVENS: So --

DR. HUDAK: I'm sorry.

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

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

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

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

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

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

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

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

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

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

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

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

DR. HUDAK: Responses to that?

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

DR. HUDAK: Go ahead, Peter.

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

about?

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

DR. HAVENS: Thank you.

DR. HUDAK: Dr. Zuppa.

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

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

DR. NELSON: Three paragraphs.

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

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

DR. HUDAK: Dr. White?

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

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

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

that received twice the regular dose?

DR. MULUGETA: Exactly.

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

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

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

days. And those are levels that are below, you know, what Dr. White quoted as the

percent where you begin to experience some signs or symptoms. So, you know, with four cases with these doses, I'm not sure that we have enough information really to be helpful to people.

DR. HUDAK: Dr. Zuppa.

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

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

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

DR. KISHNANI: No.

DR. HAVENS: No. Thank you.

DR. HUDAK: Okay.

DR. KISHNANI: Thank you.

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

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

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

DR. KISHNANI: I agree. Date not sufficient.

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

DR. CNAAN: Data not sufficient. No.

DR. ZUPPA: Data not sufficient. No.

DR. CALLAHAN: Dr. Callahan. Yes.

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

DR. MOORE: Erin Moore. No.

DR. CATALETTO: Mary Cataletto. No.

DR. WADE: Kelly Wade. No.

DR. ANNE: Premchand Anne. No.

DR. KASKEL: Rick Kaskel. No.

DR. SAYEJ: Wael Sayej. No.

DR. TURER: Christy Turer. No.

DR. HUDAK: Dr. Nelson.

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

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

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

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

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

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

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

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

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

DR. HUDAK: Dr. Wade.

DR. WADE: I would just add that this

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

study.

DR. HUDAK: Dr. Zuppa.

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

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

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

dosage duration relationship to carboxyhemoglobinemia?

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

Sorry.

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

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

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

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

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

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

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

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

DR. KISHNANI: This is Priya. I agree.

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

DR. HUDAK: Dr. Turer.

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

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

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

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

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

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

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

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

DR. CALLAHAN: David Callahan. Yes.

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

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

DR. HUDAK: Dr. Nelson.

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

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

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

(Recess)

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

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

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

products.

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

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

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

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

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

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

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

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

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

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

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

And we are specifically interested, for

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

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

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

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

In the same way, some patients may have

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

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

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

or survives in response to a therapeutic intervention.

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

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

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

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

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

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

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

Ultimately, the goal here would be for

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

safety and/or advocacy studies.

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

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

majority of which were related to drug metabolism and transport.

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

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

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

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

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

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

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

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

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

So what we decided to do is to go

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

subject study so that was in August of 2016.

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

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

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

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

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

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

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

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

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

So we basically have evidence derived

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

Now we also understand that this isn't

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

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

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

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

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

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

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

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

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

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

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

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

The last example I'll walk through is

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

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

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

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

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

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

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

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

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

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

So from a pharmacokinetic and response

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PACANOWSKI: Sorry.

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

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

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

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

DR. WHITE: Okay, thank you.

DR. PACANOWSKI: Okay, thank you.

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

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

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

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

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

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

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

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

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

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

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

And clinical validity, does my test

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

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

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

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

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

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

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

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

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

which genotypes are PM (poor metabolizers) and for example, should intermediate metabolizers be included?

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

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

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

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

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

We see that different laboratories have

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

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

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

DR. KELM: Thank you.

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

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

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

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

So first, my disclosures: I try to avoid interactions with the pharmaceutical industry because it makes my annual reporting as a special government employee very difficult. The purpose of the waiver was this atomoxetine study that was supported by an RO1 grant from the National Institute of Health. And in fact, some additional work that -- where we are taking that particular study now, is supported by that grant at the bottom of the slide. It's a U54 grant from NICHD and we are one of four specialized centers for research and pediatric and developmental pharmacology.

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

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

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

not knowing what we don't know.

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

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

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

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

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

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

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

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

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

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

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

need to have their dose reduced or increased?

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

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

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

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

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

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

So there were subtle differences but the

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

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

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

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

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

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

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

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

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

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

One of the things that I didn't mention

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

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

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

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

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

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

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

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

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

like pimozide where both CYP2D6 and CYP3A4 are important.

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

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

Extrapolation of adult data to children. We have within a group a number of pediatric subspecialists and the data in this particular slide represented by pediatric cardiologist in the group, John Wagner, last year, at an AHA meeting, and what John is interested in is the effect of genetic variation in the SLCO1B1 gene. This is the gene that codes for the hepatic uptake transporter

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

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

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

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

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

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

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

So the concept of right exposure. So

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

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

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

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

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

differences?

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

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

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

(Track 36 concludes)

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

And then we're going to have to

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

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

respond. We don't know.

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

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

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

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

So I think our experience with the Strattera study has really pushed us towards the genotype stratified pharmacokinetic study design. And, as I mentioned, Dr. Wagner, the young cardiologist in our group, he is using a similar design, SLCO1B1 genotype stratified pharmacokinetic studies. I showed you the [Simvastatin] study. We have he's finished a pravastatin study. We're writing it up now. And we'll be finishing up a atorvastatin and rosuvastatin study probably within the next six to nine months.

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

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

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

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

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

But the value of this, there's two

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

Now, here comes the kicker though, if we

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

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

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

right.

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

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

that's going to receive the drug.

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

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

than 30.

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

[FILE 38]

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

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

In this discussion please consider the

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

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

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

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

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

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

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

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

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

all.

And I think that was all of my comments.

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

All right. Dr. Sayej.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. HUDAK: Dr. Zuppa.

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

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

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

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

DR. ZUPPA: If --

DR. HUDAK: Dr. Zuppa.

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

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

DR. ZUPPA. Okay.

DR. HUDAK: Dr. Kaskel.

DR. KASKEL: I would start with one of

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

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

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

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

DR. HUDAK: Dr. Sayej.

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

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

The other medication that I referred to

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

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

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

DR. HUDAK: Yes, please.

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

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

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

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

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

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

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

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

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

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

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

DR. KISHNANI: Yes. Can you hear me?

DR. HUDAK: Yes, very well.

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

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

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

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

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

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

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

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

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

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

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

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

DR. HUDAK: Michael?

DR. WHITE: Thank you. Michael White.

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

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

The difficulty in doing that is no one's

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

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

And that rambles a lot. Thank you.

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

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

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

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

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

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

The other issue is that for one of the studies that's come out of St. Jude looking at methotrexate pharmacokinetics and genetic variation in SLCO1B1, a transporter that not only transports statins, it also transports methotrexate. It turns out that the burden of variability is not so much common variance in the SLCO1B1 gene. It's a rare variance. And it's unlikely that you're going to capture those rare variances in just a limited genotyping platform. That's almost going to require a sequencing-based application.

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

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

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

The other answer I would provide is

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. HUDAK: Thank you. Dr. Nelson.

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

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

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

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

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

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

DR. HUDAK: Dr. Zuppa.

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

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

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

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

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

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

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

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

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

DR. HAVENS: Peter Havens.

DR. HUDAK: Peter. Go ahead.

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

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

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

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

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

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

Ms. Moore.

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

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

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

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

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

have this medication.

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

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

So, on Ivacaftor, it might not change their sweat chloride level. However, it's helping them to gain weight, which is helping them to grow. It's declining the rate of exacerbation that they have. But when they're tested and the medication is not showing that it's changing the endpoint that's being measured, insurance is denying access to that medication. So, it's

tricky.

DR. HUDAK: I think it was tricky for FDA to go through the approval process for the latter medication.

Yes?

DR. JONES: Bridgette Jones. Another thing I'd like to point out regarding discussing the results with parents and families and explaining to them the results -- usually we'll try to just discuss what the results mean for the specific drug they referred us to, but as you all know, these metabolizing enzymes metabolize numerous drugs. Then questions come up about: Well, if I have this genotype then how will it affect, you know, A, B, or C drug. And depending on how what other pathways are involved in those drugs and transporters and receptors, the answers may be different. So, it makes it even more complex. And so sometimes we'll ask families to contact us if they're going to use another drug that's metabolized by that same pathway. And we can provide as much information as we can, but I

would imagine that for practitioners, this would be a particularly difficult situation to navigate with families.

DR. HUDAK: Dr. Zupa.

DR. ZUPPA: I would second that. I think it's a slippery slope, because you go in and you start a discussion, and if you only have half the answers or a quarter of the answers, I think it can be not the best experience for the family and the patient.

DR. HUDAK: Maybe I can have the more specific question here. So we had discussions on four different drugs today with different language at different locations on the FDA label. Was there any one of these products that anybody thought might have been labeled differently or with different emphasis, perhaps at a different location than what had been provided on the label? That might be a concrete point of discussion if someone has a thought about that.

Dr. Wade.

DR. WADE: Just a comment that it's such

an exploratory field right now, that a lot of the information in the label obviously came in different sections if it had to do with laboratory monitoring or a side effect or dosing. And I'm just wondering, assuming that this field expands, if I had thought, oh, I think there are some pharmacogenetics associated with this drug, there's not a consistent place in the label to look for that. And one theme that has come out of this is that in the clinical practice, not everyone is well versed in pharmacogenetics, and so it may be just that we have an inkling, and I just wonder if this field expands if it would be worth having a consistent location in the label rather than having to know where the pharmacogenetics effects, drug disposition or drug toxicity is and then having to look in a specific section. I'm sure there are pros and cons of that.

DR. HUDAK: Dr. Nelson.

DR. NELSON: I'm not going to comment on that directly, but let me make an observation in

pediatrics and then see if Mike has some thoughts on that.

In pediatrics, for example, you know, pediatric studies done under BPCA and PREA that you see here in terms of the post-marketing Pediatric Focus Safety Review, if the drug does not get the indication then in Section 8.4 I think it is -- or is it -- yeah, 8.4, you'll see a description of all the pediatric information there. But if it gets the indication, the data will be dispersed in whatever area of the label it should be, whether it's indication, dosing, safety. Because they've gotten the indication, the assumption is you'll look at the whole label. Maybe that's incorrect, but the assumption is that one will look for that data.

Now whether that's an appropriate model for pharmacogenomics or not I think is an open question. And certainly since this is closely related to clinical pharmacology, there is a clinical pharmacology section. So, I'm not sure what the thinking is. I honestly don't know what

the thinking is in terms of where that was dispersed in labeling or whether it's similar or different from the pediatric thinking.

DR. HUDAK: Mike Pacanowski?

DR. HAUSMAN: Yeah, I'll just --

DR. HUDAK: Oh, I'm sorry, go ahead. You're first and then Dr. Hausman.

MR. PACANOWSKI: Sure, just to build on what Skip had said. If there are specific dosing instructions, that will typically fall under dosage administration, or if it's a clear untoward effect, it'll end up in contraindications or some other more permanent area of labeling. There is a section, a subsection, of clinical pharmacology where data and more transparent presentation of information is often presented. We typically don't put the dosage or usage instructions down there, because it's buried in the label. But it cross-references with other sections of labeling.

DR. HAUSMAN: Hi, Ethan Hausman. I was going to say basically the same thing, but I would add on that for failed studies when the

information is limited to Section 8.4, what we generally include there is a description of the study, but we try to avoid any appearance of implying an indication.

So, in that scenario, we might not even provide comprehensive safety information if it has been similar to studies in other populations, like adults. It might be distilled to a simple sentence that safety and effect -- safety was similar.

In the scenario which we don't imply frequently but we do occasionally, if there is a new safety signal in the pediatric study that failed, we will describe that in Section 8.4. So, one might supposed that in a failed study if data were good, if there was an adequately performed study, and it just happened to not show effectiveness, if the data were actually acceptable I could envision a possibility where some pharmacogenomic/pharmacogenetic data might make it into 8.4. But generally if the study has failed, we keep that description very, very brief.

DR. HUDAK: Dr. Turer and then Dr. Kaskel.

DR. TURER: So, as a primary care physician, I think that a lot of this is not used in pediatric primary care. Because I'm also a practicing internist, I think in internal medicine we've learned a lot of lessons about many of these interactions, which may provide some insights.

So, for example, with warfarin, when we looked at the benefit of doing the genetic testing in well-conducted studies, it didn't really impact clinical care.

In contrast, I think the data were very compelling for efavirenz. I think that's a great example of, you know, they did the trials; they showed that that made an impact. And I think that it partly has to do with the severity of the adverse effect that you're trying to prevent -- the ability to predict the response based on whatever the, you know, the genetic mutation is, and then the availability of alternative therapy.

And for that final one, I think Plavix

is actually a very interesting case in point, because we administered in these very acute situations, and for a very long time it's the only one that we did administrative in the cath lab. And so then there were a number of studies looking at these genetic interactions. But by the time they came out, then we had a whole host of alternative drugs. So, now it's kind of a moot point in terms of Plavix.

So, I think, you know, thinking really smartly about what are the drugs that have been in use for a very long time that we could really be helped by in primary care and throughout out, I echo -- I think steroids are one of them.

And then the final thing -- so, things are in practice for a long time that are not going to time out -- the final thing, I think our patients read the labels. Physicians don't. And I am struck by the number of patients that come to me after I've prescribed a drug and say: You know, I was going through the label with the pharmacist, and it says X, Y, and Z.

So, I think it's very important to get -- you know, we have a lot of physicians on the panel but also the patients, and how to -- if that information is in the label, how do we pull the patient into this conversation? And until we do that, I don't know that -- you know, I would submit that we're not ready to put it in there unless we have fantastic data like the efavirenz. We have a drug that is not going to time out. A clear response, the ability to predict response, and a way to communicate with patients about it in a way that makes sense.

DR. HUDAK: So, Dr. Kaskel is first and then --

DR. KASKEL: Recently I learned about a special population of children who may need to be treated with allopurinol, and it was a response to an NIH RFA for treatment of children with chronic kidney disease. And we submitted an application, and someone brought up on the call that allopurinol has a risk factor. If you're of Asian descent you can develop a very, very severe

cutaneous reaction. Very severe. And it's associated with HLAB5801 allele.

It was news to me. We don't use allopurinol all that much, but this NIH study is trying to address treatment of uric acid abnormalities in children who seek AD, because it hasn't been studied. So, it turns out that the FDA label does not discuss this risk. No one knew this except one person on the call who said: You'd better look into this and put in your application that you're going to screen every subject in the study, if you're granted, for this allele.

It is listed in the CPIC. It recommends testing before treatment. So, here's an opportunity with a drug that's been around for a long time, not used for gout in children very often but now is being promoted to be used to prevent cardiovascular disease in children with CKD -- mild to moderate CKD. And the information isn't there. And what I would envision at some point, when we go into our EMR and we prescribe

that drug and the EMR has the ethnicities in it already, up comes a little tab that says: Hello, you need to test for this. And I certainly wouldn't have known this nor told the parent that we need to test for this. Just an example.

DR. PORTMAN: This is Ron Portman. I like Steve's vision of the future, and I just want to say that I think that in 10 years this discussion will be very different. I think that most large pharma at least have departments of precision medicine, and much of what we're doing in developing new drugs is considering the concepts of precision medicine rather than taking a drug that only 50 percent of patients responded to and just saying: Well, that doesn't work out. Now the question is: Why did only 50 percent respond and begin to explore some of these pharmacogenetic issues? And I think that the idea that we were seeing cancer with codiagnostics is going to be present in many drugs in the future.

DR. HUDAK: So, I think we have, as usual, a robust spread of thoughts on this

particular issue, and I can see both points of view as to too much or too little information on this. I tend to air on the -- maybe, too much information, because it is information that can be hopefully dealt with. But that's a good point about the allopurinol.

You know, it's interesting the approaches that pharmacies have across the country to this. You know, St. Jude's, I referred to before, has this program, and their approach to the codeine issue was they tested all of their -- you know, not all of their -- 80-something percent I think of their sickle cell patients, who are the bulk of the patients who were prescribed codeine, were tested. And the pharmacy systems came up with alerts. I mean, it said: If this patient is an ultra-rapid metabolizer, don't give the drug; here are some alternatives. You know, they had 20 percent where there was no information and the physician was warned, you know, no information, don't know. And so they had a very good -- this has worked very well. They had, really, only one

case in which a possibly at-risk patient was treated with codeine, and that turned out to be by physician discretion, because that patient had received codeine before and had no, you know, no issues.

Other hospitals, like Boston Children's Hospital, they dealt with the codeine problem by just removing it from the formulary, because there are other drugs that are as safe and effective -- as effective and more safe or safer. So, there's a huge variation, I think, in practice on this.

DR. HUDAK: Any other comments? Dr. Havens? Dr. Kishnani, anything else?

DR. HAVENS: Thank you. It's been a rich discussion. I appreciate it.

DR. KISHNANI: This is Pryia. I have a comment.

DR. HUDAK: Go ahead.

DR. KISHNANI: Mike, I'm glad that the topic of allopurinol came up. It almost became medical legal at our university at one point, and so one of my questions and concerns is that this

is definitely an evolving field and, yes, we must have it on the label, but it must be in a place, you know, where it's easily available or seen. But, on the other hand, it also gives leverage from an insurance company reimbursement perspective, because I think otherwise we end up opening ourselves up, that if we prescribe certain medications which end up with a complication and if it's not in an identified spot in the label, we could get in trouble. So, I do believe that we have to do these things, but it has to be done in a systematic way so that, you know, as physicians not only are we equipped but we are also covered.

DR. HUDAK: Yes, thank you for that.

DR. HAVENS: Peter Havens.

DR. HUDAK: Yes, Peter.

DR. HAVENS: For abacavir, the HLA association with hypersensitivity is in a boxed warning. So, it's very clear. But, as we talked about with abacavir, that's mostly for whites. Here you're making a pharmacogenomic requirement that mostly applies to Han Chinese. And so it

shows the complexity of trying to do this. You would argue, consistent with the abacavir, that you'd want it in a boxed warning. But then are you going to apply it to everybody, or are you going to only apply it to Han Chinese, the population within which it's been found to be an issue?

DR. HUDAK: Excellent question. I have the question for Dr. Nelson, so the first question is: Your impression of the field in terms of the rapidity with which information is being generated now, the anticipation of the trajectory of this in the future, and what mechanisms FDA might be able to have should you decide to be more generous in providing this information in label form. You know, with some journals, like Pediatrics, they do not allow in certain articles publication in print of tables or whatever with information that can change rapidly. So, their policy is basically to put a URL in there, that you can click on the URL and it'll provide you with up-to-date information

because it may change every couple of months, rather than memorizing something that's going to be out of date by the time the journal comes to press. So, I don't know to what extent that sort of approach might be something that would meld with this rapidly expanding field in the future. For you, just some comments.

DR. NELSON: So, let me just give some thoughts about what I've heard, and this is just what I've heard, not necessarily what FDA has heard, and I'm not sure what it means to say what FDA hears or not, frankly.

You know, there's I think a promise of pharmacogenomics that everybody recognizes to the extent to which precision medicine could ideally offer improved efficacy and decreased adverse drug effects. If you get the right exposure and don't necessarily end up with the variability that we get by just picking dose, and I heard -- and I certainly heard the theme of what drugs would we love to have these data on would be those that we see this great variability in response, whether

it's corticosteroids or others, that it's not that we necessarily have those data now, but could we understand that variability better.

Now, I doubt we would eliminate all variability by getting these data, but that would be something to be gained. I find it challenging to think about what I think Steve challenged us to think about is -- you know, when we think about phase 1, early phase trials is to get the dose right. What he's really saying is maybe we should start thinking about getting the exposure right and maybe that's going to require pharmacogenomic thinking to be able to get the exposure right.

But how that gets incorporated into study designs at this point I think is a complex question. I mean, he offered some suggestions for pharmacogenomic stratification, if you will, of early PK testing, but I think, you know, I would have to sort of take that back and think about that with people who have thought about that a fair amount. But optimizing exposure I think is what we're all about in thinking about the right

dose to the right child at the right time.

What makes that more complex, you know, so we would think of exposure ranging instead of dose ranging. We often think of dose ranging as what we have to do in a trial boon. What makes that complex, then, is pulled into the autogeny of the target -- and to the extent that might be changing. So, you not only have -- you know, you're changing how much you're putting into the organism, but you're also changing what you're trying to hit at the same time, and that may be more of an issue for infants and younger children. It may not -- I don't know. It depends on the disease; it depends on the drug.

So, I've certainly heard that there are substantive differences when you look at the different drugs, when you look at the different metabolic pathways. Are there alternate pathways? You're looking at the disease. You're looking at the population. You're looking at genetics of that population. It's clear that one size is not going to fit all in this area. And I agree with

Ron that this is going to be a moving target, you know, as the cost of the ability to do these tests comes down.

I won't mention the company, but for a present I was given my -- I sent my DNA and got it back last week, you know, heritage and things, and I'm pleased to say I'm not at risk for early Alzheimer's. But I knew that was my family history anyway, so it wasn't -- it didn't add a whole lot. But, you know, you can get all of this, and I was able to download my genome and then upload it into heritage.com. Well, oops, sorry, don't have any stock in that either. (Laughter) But anyway, to do that was sort of fun, you know, and that was $250. So, I'm assuming that this technology will be coming down in price, and the point at which you're able to show that you save money by improving efficacy and degaussing adverse events, I would be interested if the institutions that are starting to do what Steve says Children's Mercy is thinking about -- predisposition or, you know, not just forensic

testing but prior testing -- to show that within that system costs have been -- I'm assuming then that would begin to get to the point where it would compel people to do it, not only in clinical decision-making but in the cost effects.

So, from my point of view, I think the challenge for FDA is, you know, we're not into costs -- that's not our remit -- but the question is: How can we incorporate some of this thinking into prospective study design? You heard from Mike's presentation often that comes in sort of in the post-approval phase. But how much of that can be done up front? How much do you know up front? You may not even know it until you begin to see that variability.

I could go on, but those are some of the themes that I heard in terms of the complexity of this area. And, frankly, I think part of the intent of not -- when we got into the discussion of favorance at the previous meeting was to imply, yeah, this is more a complicated area than just saying: Well, we ought to throw something into

the label. So, I think we showed that. (Laughter) I think we demonstrated that. It's a lot of information, so it's -- but, you know, I think everybody, at least from the FDA, may have taken different themes aside: We'll take it back, we'll think about it. But, you know, there wasn't any real deliverable here in terms of what we were thinking we would do to change our practice. That was not the intent, it was to have a discussion that would hopefully both inform you and inform us about the complexity of this area. So, I think we've achieved that at the very least.

So -- I know, welcome to entertain any other comments, but those are my thoughts -- again, just my personal thoughts -- listening to the conversation.

DR. HUDAK: Dr. Wade?

DR. WADE: Skip, can you -- Kelly Wade -- can you comment on what was raised about allopurinol, because it struck me as well that pharmacogenetics changes over time and how we use it and who's its advise. But labels don't change

in real time. You know, they're not as easily updated. So, what resonated with you in that allopurinol discussion?

DR. NELSON: Well, so, labels are a complex area, but if there is something that requires a labeling change based on safety, FDA has the authority to do that. I don't know enough about that. I mean, I guess the question would be the extent to which that information tracks phenotype -- in other words, should that -- Peter's comment I thought was very interesting, and I didn't know that about abacavir. It's in there as a warning, and so everybody gets tested even though it was developed in Australia and it's applied to African- American heritage and so on and so forth. So, is that going to be the same issue with allopurinol if it's found in this population? But then we put it somewhere and then everybody gets tested.

I don't know the answer to that question. I think it's an interesting set of issues. But I would hesitate to say anything

other than, you know, I think it's worth thinking about, but if FDA concluded we should change a label for safety reasons, I know we have the authority to do that, but whether that's the right thing to do or not, in that case, I would not comment on.

DR. HUDAK: Dr. Sayej?

DR. SAYEJ: I would just like to make one final comment. If the FDA decides on making sure that all -- well, everyone's goal is to make sure that the patient and the prescribers are well informed of every detail about the medication that they're prescribing or taking and making sure that the patients are safe. So, providing this information in the label is very important. So, if there's a drug that has a test that can potentially prevent adverse events or further complications, then that's great. We need to have that test available, and we need to be able to order that test.

Unfortunately, that's not always the case. These tests are not always commercially

available, and doctors struggle to figure out where to send these tests or how to get them covered and how to monitor or the tests for monitoring are not covered. And so if we -- I think we have to take into consideration all of these aspects and not just, you know, what is the label going to say: Well, what are the implications on clinical practice? What are the implications on cost to the patient? What are the implications on the physician's practice? You still don't want to throw the physicians under the bus by saying: Oh, well, this isn't labeled; you need to check this before you start the patient on the medication.

We all know that we prescribe medications all the time off label, and physicians do that every single day in their practice. So, what I'm trying to say is we need to take all these things into consideration and really kind of make sure that if we enforce something like this, we have the resources where patients and physicians can follow through with this

medication.

DR. HUDAK: Dr. Callahan.

DR. CALLAHAN: Yeah, I just want to make a comment about the carcinogenic testing.

So, I work in an outpatient setting in an outpatient practice. I'm not tied to a hospital, and I no longer order my genetic testing through Washington University, because they don't want to do the work to get it covered, and our genetics department is the same.

But if you're not in an institution, it's very easy to get good genetic testing through many labs. I can get you the names if you want them. And you send them the information. You send them the requisition. You send them the insurance. You send them the diagnosis. And they won't require your staff to do it. They'll do the work. They'll get it covered. Or they'll do it for a hundred dollars just to do it, because they want to provide genetic testing. But I think when you're with institutions they're going to charge the institutions as much as they can get out of

them.

So, I do go to Shriners Hospital once a month. We have a neurology clinic there, and we need genetic testing, but Shriners won't pay for it, because it ate up all of their budget to do their orthopedic surgeries. So, I download the requisitions online. I give them to the patients. I check the box "Benefits Analysis" first. They take it to an outside lab, paste in the sample and the blood, and that lab will contact the patient of what their deductible is, and I've never had a patient that has had to pay more than a hundred dollars for next-gene sequencing for some complex testing.

And the same thing with pharmacogenetic testing. When they come to our office, they say the maximum they'll change a patient is $300. Now, that -- I'm sure they'll charge much more if you send it through your institution. They'll charge the institution as much as they can get.

DR. HUDAK: Dr. Nelson.

DR. NELSON: I have two comments. So, I

think if you look back Mike Pacanowski's slides, he talked a lot about the uncertainty, about the place of this testing, and the context of the clinical decision-making, and so I think we're certainly in agreement that the decision to put something on the label has to take into account the factors that you outlined in terms of the complexity, the physician decision-making, and so on and so forth.

And I will say, anybody who wants information about that kind of testing, I suggest you do it after the meeting. You can certainly check with Dr. Callahan about the availability of that testing since the FDA shouldn't be a part of that exchange.

DR. HUDAK: It does bear a comment, because it is part of our daily lives, and specialists don't have to deal with some of the implications of all of this. Primary care physicians often times do because of the attribution of cost -- the primary care provider that may determine, you know, how well they do.

It's a real issue, yeah.

DR. NELSON: All right, Skip Nelson again. Who we knew it was, which is why on the first question we alluded to please talk about the challenges. So, we were not blind to the fact that there are those challenges. All I'm suggesting is if you want specific advice about the company to contact, I suggest you do that after the meeting is over, over dinner or whatever.

DR. HUDAK: All right, any other thoughts? If not, I think on behalf of the committee, we want to thank Dr. Nelson for organizing this program and the excellent speakers from FDA and Dr. Leeder from Missouri who educated and enthralled us with a lot of information today, and even though we haven't come to definite conclusions, it certainly informs us going forward. So, thanks.

(Whereupon, at 4:59 p.m., PROCEEDINGS were adjourned)

* * * * *

CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the Commonwealth of Virginia

My Commission Expires: November 30, 2020

Notary Public Number 351998