UNITED STATES FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Bethesda, Maryland

Wednesday, September 14, 2016

PARTICIPANTS:

Welcome and Introductory Remarks:

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

Introduction of New Designated Federal Official and Award Presentation:

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

Opening Statement:

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Center for Drug Evaluation and Research (CDER) (Sustiva):

CAROLYN YANCEY, MD
Division of Pediatric and Maternal Health
Center for Drug Evaluation and Research
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PARTICIPANTS (CONT'D):

Update on Exjade (deferasirox):

PETER WALDRON, MD
Division of Pharmacovigilance
Office of the Commissioner
Center for Drug Evaluation and Research
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Abbreviated Presentations:

MENVEO (Meningococcal(groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine

JUDITH U. COPE, MD, MPH
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IXIARO(Japanese encephalitis vaccine):

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Topamax (topiramate):

MONA KHURANA, MD
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Office of New Drugs
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Asacol & Asacol HD, and Delzicol (mesalamine):

LCDR ERICA RADDEN, MD
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PARTICIPANTS (CONT'D):

Kepivance (palifermin):

LCDR ERICA RADDEN, MD
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Bloxiverz (neostigmine methylsufate):

AMY TAYLOR, MD

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Doryx (doxycycline hyclate):

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Xolair (omalizumab):

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Karbinal ER (carbinoxamine maleate):

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Pregnancy and Lactation Labeling Rule (PLLR):

MIRIAM DINATALE, D.O.
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PARTICIPANTS (CONT'D):

Tutorial - Review postings of the web:

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

Annual Post-Market HDE Reviews:

Berlin Health EXCOR Pediatric Ventricular Assist Device (VAD):

REBECCA WARD, MPH
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Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Diseases and Radiological Health
Food and Drug Administration

CONTEGRA Pulmonary Valved Conduit:

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Pleximmune:

KELLIE KELM, PhD
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PARTICIPANTS (CONT'D):

Enterra Therapy System:

CATHERINE RICKETTS, RN, BSN
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Elana Surgical Kit (HUD):

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Wrap-Up and Adjournment:

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P R O C E E D I N G S

(8:02 a.m.)

DR. HUDAK: I'm Mark Hudak. I'm the Chair of this committee and will be chairing most of this meeting. I'd like to welcome everybody today. Our usual order of business to start with is we have a number of new members. Some people who are new and official, but they've been here before.

So maybe we can go around the table and introduce ourselves? Thanks.

DR. FISCHER: Thank you. Gwen Fischer from the University of Minnesota. Pediatric Critical Care and this is my first meeting.

MS. JONES: Hi. I'm Bridgette Jones. I'm the pediatric healthcare representative from the AAP.

DR. MOON: Hi. I'm Mark Moon. I'm a cardiothoracic surgeon from Wash U in Saint Louis.

DR. SAVEI: Hi. I'm Dr. Wael Savei, pediatric gastroenterologist from the University of Connecticut.

DR. HAVENS: Peter Havens, pediatric infectious diseases from Medical College of Wisconsin.

DR.Turer: Christy Turer, primary care from University of Texas Southwestern.

DR. SHWAYDER: Tor Shwayder, pediatric dermatology, Henry Ford Hospital in beautiful, downtown Detroit.

DR. CNAAN: Avital Cnaan, statistician, Children's National. From beautiful D.C.

DR. CATALETTO: Mary Cataletto, pediatric pulmonology and sleep medicine, Winthrop University Hospital in New York.

DR. CAMPBELL: Jeff Campbell, pediatric neurosurgeon from Nemours, A.I. DuPont in Wilmington, Delaware.

DR. CUNNINGHAM: Melody Cunningham, pediatric palliative care, University of Tennessee in Memphis.

DR. HUEHN: Sarah Huehn, pediatric critical care, palliative care, University of Kansas.

DR. DRACKER: Bob Dracker, pediatric hematology and transfusion medicine, Syracuse, New York.

DR. BRILL: Marieann Brill, DFO, OPT.

DR. WHITE: Michael White, Oschsner Health System and University of Queensland Clinical School in New Orleans.

DR. WADE: Kelly Wade, Neonatologist, Children's Hospital of Philadelphia in Philadelphia.

DR. ANNE: Premchand Anne. I'm a pediatric cardiologist from Saint John Providence Children's Hospital in Detroit.

DR. COPE: Judy Cope. I head up the safety team for the Office of Pediatric Therapeutics at FDA.

DR. NELSON: Skip Nelson, Deputy Director, Office of Pediatric Therapeutics, FDA.

DR. HAUSMAN: Ethan Hausman, division of pediatric and maternal health, FDA.

DR. ALEXANDER: John Alexander, Deputy Director, Division of Pediatric and Maternal

Health, FDA.

DR. HUDAK: Okay. Welcome to all the new members and we hope to have an on-time meeting. As at this point I'll turn it over to Marieann as our DFO to read the required statements.

DR. BRILL: Thank you, Dr. Hudak, and good morning everyone. The following announcement is made to address the issues of conflict of interest with regards to today's discussion of reports by the agency as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act.

Based on the submitted agenda for today's meeting and all financial interests reported by the committee participants it has been determined that those individuals who will be participating in each topic do not have a conflict of interest for the following products: Exjade, Asacol, and Asacol HD, Bloxiverz, Delzicol, Doryx, Karbinal ER, Kepivance, Sustiva, Topamax, Xolair, MENVEO, IXIARO, Pleximmune, Elana, CONTEGRA,

Enterra Therapy System, and Berlin Heart.

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

In order to provide the scientific and latego perspectives required to adequately address the products covered in today's meeting. The following individuals were invited to participate as expert consultants and are considered temporary voting members on the committee: Dr. Mark Moon, Dr. Ken Towbin, who will be joining us via phone, Dr. Gwen Fisher, Dr. Premchand Anne, Dr. Jeffrey Campbell, Dr. Wael Savel, and Dr. Tor Shwayder.

Dr. Bridgette Jones will serve as the healthcare representative and that is a non-voting position. Dr. Maldonado who is our industry rep, will not be able to join us today since he is traveling from London. Therefore, based on an analysis of all the reported interests that we received prior to this meeting we have the

following recusals: Dr. Mark Moon will be recused from the discussion of Enterra Therapy System. Dr. Bridgette Jones will be recused from the discussion of Karbinal ER.

Dr. Mark Hudak will be recused from discussion of Sustiva. Dr. Gwen Fisher will be recused from the discussion of Berlin Heart. At the time the product comes up for discussion, these individuals will simply step away from the table. With respect to all other participants we ask, in the fairness -- in the interest of fairness that they state any current or previous financial involvement with any firm whose product they may wish to comment on.

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

As a reminder to the committee and those around the table, this meeting is being transcribed, and as such, when you are acknowledged to make a statement or have a question, if you would please press the button on your microphone and state your name prior to the beginning of your statement.

I would also like to remind the members of the committee and audience to please silence your cell phones to minimize interruptions during the meeting. One last thing I'd like to point out of due to a business schedule ahead of us today we may need to make some time adjustments to the agenda. We ask the speakers to please be mindful of the duration of their discussion or their presentation so that we stay in the target for the agenda.

One last announcement, for those Pediatric Advisory Committee members who are joining the meeting tomorrow, Euneka will be here. She will meet you in the lobby by 6:30 tomorrow morning and she will procure four cabs to bring

you to White Oak for the off period meetings. Please look out for an email from Euneka as well.

At this time I'd like to turn the attention over to Dr. Hudak.

DR. HUDAK: Okay. We have one other significant point of business in the introductions today. We do have a significant absence this morning due to conflicting schedule, but Dr. Dianne Murphy who is the director of the Office of Pediatric Therapeutics is not here today.

She has been the guiding light for this pediatric therapeutics development since she came to the FDA in 1998. She's been here through all of the abbreviations that have taken place, FDAAA, PDUFA, and PREA, and BPCA, and FDASIA. She was in place when this committee first came into being, actually as a subcommittee to the pediatric infectious disease, I think, committee.

So she has done remarkable work. She's been recognized nationally and internationally. She received a very prestigious award from the American Academy of Pediatrics in 2013 called the

Excellence in Public Service Award. Past recipients of that award have included people like Michelle Obama, David Kessler, the late Senator Edward Kennedy, Henry Waxman, and so forth. So she's in a very elite group with that award, well recognized by her home organization the AAP.

She also, last year, 2004, I guess, received the Francis Kelsey Award from the FDA which was inaugurated in 2010. So her staff actually selected an award here for her. This is one that will be presented to her, I'm sure, in another ceremony. But I think on behalf of the staff and all of the current and prior members of all former committees I'm very happy to announce this award here.

It's to Dianne Murphy for her unrelenting support and dedication to the health and well-being of children. So there will be a separate ceremony, I'm sure, for Dianne, and for those of you who don't know, Dianne is leaving the agency, retiring, to do other things. Somewhere around the end of October of this year. I'm

dubious about that because in talking to Dianne she says that she has so much work to do that I'm not sure she's going to get it done by the time, end of October, so we'll see what happens.

Moving on to business here. We thought we would move up Dr. Towbin's presentation which is scheduled for a little later in the afternoon, since we have some extra time here before the open public hearing. So, Dr. Towbin.

SPEAKER: Quinto.

DR. HUDAK: Quinto, sorry. Kenneth. Stick with first names.

DR. QUINTO: Good morning. I'm Lieutenant Commander Ken Quinto, a medical officer in epidemiology and the Office of Pediatric Therapeutics, OPT, and I'll be presenting the Pediatric Advisory Committee Risk Base Assessment Review procedure.

Our presentation will follow the outline noted in this slide. First I'll present a brief review of the risk based assessment. Next I will provide an overview of the procedure to review web

posted safety reviews, and submit comments to the open docket.

First, a brief review. During the April 2016 PAC meeting I first present the risk base assessment to the Pediatric Advisory Committee. In essence, the risk base assessment is a modification to PAC review for certain CDER products that are designated low safety risk.

The factors that determine low safety risk CDER products were built from previous criteria, used for abbreviated presentations to the PAC. This is a timeline for the risk based assessment process. After the data collection for the FDA adverse event reporting system, FAERS, collects adverse event reports, the internal review team, consisting of members from OPT, the Fivision of Pediatrics and Maternal Health, the Office of Surveillance and Epidemiology, and the appropriate CDER division attend meeting one.

During this meeting, the team discusses a plan to review FAERS cases and drug utilization data. Prior to meeting two, the Pediatric

Post-Marketing Pharmacovigilance and Drug Utilization Draft Review is circulated. During this meeting the team discusses a draft review of the FAERS cases, and of the results of a drug utilization data analysis.

Near the conclusion of this meeting the team will decide whether a product is a low safety risk product or not. If the product is designated as a low safety risk product it follows a process, noted in green, to the top portion of the slide. If the product is not designated as a low safety risk produce it follows a process noted in red in the bottom portion of the slide.

During meeting two the review team considers the following factors in determining whether to designate the produce below safety risk. Number one, no pediatric deaths or pediatric deaths likely attributable to disease progression. Number two, no or few serious adverse events, SAEs attributable to the produce.

Number three, no new safety signals identified by FDA through literature review, FAERS

case review, drug utilization data review, and ongoing track safety issues for product or class of products. Number four, product adequately labeled for pediatric use, including dosing information, and adverse events included on product label. Number five, there is little pediatric use or the number of adverse events relative to use it not concerning.

As I previously stated, the factors that determine low safety risk CDER products were built from previous existing criteria used to determine abbreviated presentations to the PAC.

This is a timeline for the low safety risk product. As of two days ago we are now in the last phase of the low safety risk product timeline. Reviews for the four CDER products have been posted to the FDA website, and the docket is open to receive comments until Friday, September 23.

I will not explain the procedure for reviewing the web posted product safety reviews and submitting comments to the docket. The first

address noted here is the direct link to the web posted safety reviews page. This address is an address that we use for all current and future web posted safety reviews.

It is fairly simple to find the direct address of the web posted safety reviews by going to www.fda.gov/pediatrics which brings you to the OPT homepage or you can also search, 'FDA pediatrics'. This is the OPT homepage. Scrolling down to the bottom of the OPT homepage you will find a direct link to the web posted safety reviews under the advisory committee meeting subheading. The link is appropriately names, 'web posted pediatric safety reviews', and noted in the red box of this screenshot.

This is the web posted pediatric safety review page. It has a product name on the left column, the link to the safety review in the middle column, and the link to the open docket in the right column. When you click on the product safety review link in the middle column you bring up the products pediatric post-marketing

pharmacovigilance and drug utilization review.

When you click on the docket link on the right column you arrive at the open docket at regulations.gov where you can submit your comments. After clicking the comment now box, which is noted in red you will arrive at the comment forum where you insert your comments, upload any files, if necessary, and include your name and contact information. Then click continue.

You'll be then be able to preview your comment and obtain a receipt of your comment after submission. The docket will remain open for comments until Friday, September 23. Thank you for your attention.

DR. HUDAK: Can I have one question? Are these comments that come in available and archived for the public for past September 23 or just accessible to FDA?

DR. QUINTO: So we will be receiving, from what I understand, we will be receiving comments and logging the comments. We will be

looking specifically for data relative to the reviews that will make us reconsider our conclusions to the reviews, so opinions that are not supported with data will be logged, but we review any specific data or evidence that comes in to take a look at the reviews, and to make sure that in evidence of light new data that we should consider bringing the product to the PAC in collaboration with the internal review team to be making that decision.

DR. HUDAK: Any other comments, questions around the table? I think this is a nice evolution of the process. It does become much more efficient. We have a huge backload, I think still, of products to assess and review, so I think this does help. Thanks very much.

DR. QUINTO: Thank you.

DR. HUDAK: Okay. I think we will move on to the open public hearing. We have one speaker who has registered. Craig Butler who's the national executive director of the Cooley's Anemia Foundation. Is Mr. Butler here? Yes.

Good morning. Mic is yours.

MR. BUTLER: Good morning. My name is Craig Butler and I am the national executive director of the Cooley's Anemia Foundation. I would like to thank you for the opportunity to address the committee this morning. I'm here today because I know that this meeting will include an update on the FDA's ongoing analysis of a possible safety signal regarding the use of Exjade or deferasirox in children with fever.

This is a matter that we first raised with this committee at the last year's meeting on September 16, 2015, and we are pleased that an update will be given today and are anxious to hear the details of the FDA analysis. As you know from our previous testimony, we hope for a recommendation for a label change for the drug concerning interruption during times of febrile illness, and for the need for continued monitoring of this medication among the pediatric population.

As representative from the Foundation related during their appearance here last fall, we

were motivated to request these actions due to the tragic passing in January of 2015 of Zana Connelly, a thalassemia patient, shortly before her third birthday. While the circumstances which brought about this sudden death are complicated. The fact that a high fever was present during a period when the child was receiving chelation therapy via Exjade is troubling, and has raised significant concern among the thalassemia community, especially among parents of young children.

Many patients and parents express concern about remaining on Exjade after Zana's passing, but may have felt that other options are not viable for them. At our recent patient/family conference in San Diego in July this issue was mentioned to me several times.

I was able to tell them that the Foundation's medical advisory board, which consists of thalassemia experts from the major thalassemia treatment centers in the United States recommends cessation of Exjade and Jadenu, the more

recent formulation of deferasirox whenever fever is present, but that the labels for Exjade and Jadenu do not provide this recommendation.

Many patients and parents find this troubling. Not least, because a significant portion of our patient population is treated by hematologists who are not associated with a major treatment center, and who therefore, may not have had experience with thalassemia and its treatment. As a result, they may rely heavily on information from the drug label. Absent any mention of what to do in case of a fever, a doctor with little experience with the chelator might continue recommending use of the drug which could result in unwanted complications.

We know that this committee has listened to our request for guidance and we appreciate the commitment to action in this area. Please know that the Foundation is thankful for your attention and response. Your willingness to recommend that the FDA investigate an appropriate course of action is appreciated by the Foundation and by the

patients we represent.

We also gratefully acknowledge the work of Dr. Judith Cope, Dr. Peter Waldron, and members of the FDA in this area, and look forward to hearing the report later in this meeting. Thank you for listening.

DR. HUDAK: Thank you, Mr. Butler. As you point out, there will be an update somewhere around 11:15 this morning by Dr. Peter Waldron, medical officer with Division of Pharmacogivilance to talk about that.

Are there any other members who have not officially signed up for public comment? Okay. Seeing none, I will mention that there is one other comment which we received online which will be posted by the FDA at some point soon for people to see.

Okay. So we are at the point where we can begin our program. I think, Dr. Cope, you're up next, are you? For abbreviated presentations on Menveo and Ixiaro. I may be butchering that pronunciation.

DR. COPE: Okay. As I'm starting off I'm like to announce that we have representatives from the Center for Biologics Evaluation and Research sitting at the table. If you both would introduce yourself, please.

DR. ZINDERMAN: Captain Craig Zinderman. I'm the associate director of the Division of Epidemiology in the Office of Biostatistics and Epidemiology in CBER.

DR. BAYER: Bethany Bayer, medical officer in the Office of Biostatistics and Epidemiology.

DR. COPE: Thank you. So as we're starting off, I wanted to say for these two vaccines that we'll be discussing, Menveo and Ixiaro, that basically we're making them abbreviated presentations. Before I get started with that, I just want to clarify. We're basically going to put up one slide for each vaccine and very briefly discuss.

The reason is this is a process that we've been working on over the last few years, and

so I just wanted to start off by reminding people you got the background materials. But you'll see that the CBER reviews are very comprehensive. They include the adverse event reviews using the FAERS database, the post-market surveillance, the passive surveillance system that both CDC and FDA use.

Also, it is looking at the periodic adverse event reports that sponsors submit. Also, the FDA team looks at data mining to be sure there's not maybe a safety signal that emerges with the disproportional adverse event. Also, uses the utilization data and performs a literature review.

All of those, for these two vaccines show that really there were no new safety issues and basically that if there were any deaths at all they were not related to the vaccine, and that the product is appropriate label. So I just wanted to do that before we got to the two slides.

So I'm ready to show the first slide for Menveo. So Menveo is basically an active

immunization for the prevent of invasive meningococcal disease, and for the types of neisseria meningitis groups that are shown here on the title of the slide.

As I mentioned, or actually this product was licensed in 2010 and approved for ages 11 years to 55 years of age. Then in 2011 it was approved to be used in children two years and older. What's important on that was it actually came to this Pediatric Advisory Committee following that for safety review in 2012. The PAC, at that point, felt it should go back to routine monitoring or continue the routine monitoring that was done.

Now, for this pediatric meeting. What prompted this is a new labeling that takes the age group all the way down to 2 months. So that's what prompted this safety review. Now, you've got the full safety drug utilization review that's in your background materials. But, again, FDA did not see any new safety issues, felt that the product was labeled appropriately, and

actually this product had one death, but it was felt to be not related at all to the vaccination.

So FDA recommends, and they will continue for standard ongoing safety monitoring and we ask, you the committee, if you concur.

DR. HUDAK: Okay. So we'll open it up for any questions from the committee, having read the materials that were provided on this product. If no comments, I guess we will maybe just best to go around the table and get a vote. Why don't we do that?

DR. DRACKER: Bob Dracker in Syracuse. Just one question, has it been in any suggestion that indications or age for use is going to be changed at all? You know, what we're doing right now?

DR. ZINDERMAN: I'm sorry. I don't follow. Is your suggestion that the indication for use would be changed?

DR. DRACKER: There's been no recommendation yet as to change of vaccination date. Typically we use the vaccine, you know, at

11 to 12 years of age. There's no suggestion to give it at that younger age group yet, correct? To cover the smaller, you know, the initial -- because those two peaks of disease almost, obviously, are exposure. So I didn't know if there was any current consideration regarding early recommendations for administration?

DR. BOYER: So the recommendations are determined by the ACIP, the Advisory Committee on Immunization Practices, and they are the ones that have reviewed it several times, and the current recommendations are 11 years and then a booster dose at 15 to 16 years, so that's actually a different group through the ACIP and the CDC that discuss that.

But the current recommendations are just for high risk children between 2 months and up to 55 years.

DR. DRACKER: You understand my reasoning for questioning that, though? You know, with the early recommendation I wonder if we're going to ultimately use the vaccine at an earlier

age to carry that high risk group earlier on. That's why.

DR. BOYER: So I know that's been a point of discussion and it is approved down to 2 months if that is raised. That is reconsidered on a regular basis by the ACIP.

DR. HAVENS: And it's recommended in high risk groups down to age 2 months, so it is recommended in high risk groups because of their concerns.

DR. HUDAK: Okay. So to return to the question, the question for the committee is based on the information the FDA has complied in its review looking at safety. Whether the FDA should continue the standard safety monitoring process or elevate it to some other level.

So the recommendation is to continue the standard ongoing monitoring and we'll take a vote on that.

DR. FISCHER: This is Gwen Fisher. I concur.

DR. MOON: You don't vote.

DR. JONES: Okay.

DR. MOON: Mark Moon. I concur.

DR. SAVEL: Wael Savel. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. TURRER: Christy Turer. I concur.

DR. SHWAYDER: Tor Shwayder. I concur and I'm glad that you've brought it down to 2 months.

DR. CNAAN: Avital Cnaan, I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. I agree.

DR. WADE: Kelly Wade. I concur.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: Okay. So we'll go on to the second product which is the vaccine for Japanese encephalitis.

DR. COPE: Okay. Ixiaro is indicated for active immunization for the prevention of disease caused by the Japanese encephalitis virus. It's original approval was in 2009 for individuals that were 17 years and older. Then in May of 2013 it was approved all the way down to 2 months of age. That's what's prompting this pediatric safety review.

As I mentioned before, this is a single slide. As you see, you've got your full safety and drug utilization review provided in your background materials. It was a comprehensive review with all those that I had talked about before that were looked at in the review. FDA plans to continue its standard ongoing safety monitoring. We ask whether the committee concurs.

DR. HUDAK: So this is open for discussion. Okay. Hearing no questions. Dr. Dracker, do you have any comments? Okay. We'll start from this side of the room over here. Dr. Anne?

DR. ANNE: Premchand Anne. I concur.

DR. WADE: Kelly Wade. I concur.

DR. WHITE: Michael White. I agree.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CNAAN: Avital Cnaan. I concur.

DR. SHWAYDER: Tor Shwayder. I concur.

DR. TURRER: Christy Turrer. I concur.

DR. HAVENS: Peter Havens. Concur.

DR. SAVEL: Wael Savel. I concur.

DR. MOON: Mark Moon. I concur.

DR. FISCHER: Gwen Fischer. I concur.

DR. HUDAK: Okay. To summarize this for the record then, recommendations from the PAC for both of these vaccines is that the FDA continue its standard monitoring based on the initial safety review.

So we have come to a spot in the agenda.

It is 8:37. We are 23 minutes ahead of schedule. The next item on the agenda has a fixed start time of 9:00 a.m. because we're scheduled a call in from Dr. Towbin to assist us with that review. So, Dr. Nelson, Dr. Cope, do you have any thoughts other than breaking or? And any other information you'd like to present?

DR. HAUSMAN: So the presenters for some of the later products are not present, so that's part of the difficulty.

DR. HUDAK: So I guess we'll just sort of --

DR. HAUSMAN: We could -- I mean, part of it is we could move one product that Ethan is presenting if the medical officer who is supposed to be there. That's not until 2:00 though, so.

DR. COPE: You know, and we don't have the division people.

DR> HAUSMAN: That's correct.

DR. HUDAK: So I guess we'll just break until 9:00?

DR. NELSON: I think that'd be fine.

DR. HUDAK: Okay.

DR. COPE: People can rest.

DR. HUDAK: People can rest. So 9:00 we will get Dr. Towbin on the phone and resume.

Dr. Towbin, good morning.

DR. TOWBIN: Hello.

DR. HUDAK: Okay. We will get started. Our next review is on Sustiva. And just as a point of information for the remaining reviews we have on your speakers a voting system that says yes, no, abstain. So for the remainder of the product reviews we will initially use this, so it's recorded, and then we'll go around the table to solicit any additional comments that members might have.

DR. TOWBIN: And I'll be voting by voice.

DR. HUDAK: And you'll be voting by voice, right. At this point, since FDA has imputed a conflict of

interest to me I'm turning it over to Dr. White, and I will push my chair back from the

table rather than walk away.

DR. WHITE: Dr. Cope, you're not presenting this? Dr. Yancey, you're presenting this --

DR. YANCEY: Yes.

DR. WHITE: -- product for us. Thank you.

DR. YANCEY: You're welcome. Well, good morning everyone. Good morning to the committee and the audience. I'm Carolyn Yancey, medical officer in the Division of Pediatrics and Maternal Health. This morning I'll be talking with you about Sustiva (efavirenz). This will be the safety review.

This is just an outline of the topics we'll cover in this morning's presentation: background, relevant safety labeling, the pediatric studies that support the discussion this morning, pediatric labeling changes, drug use trends, the adverse events that are reported, and then our summary comments for the committee.

Sustiva is an antiretroviral agent that

is a nonnucleoside reverse transcriptase inhibitor. It's indicated in combination with other antiretroviral agents for the treatment of HIV Type 1 infection in adults and in pediatric patients at least 3 months old weighing at least 3.5 kilograms. The dose is 600 milligrams once daily, so maximum dose of 800 milligrams.

The formulation is manufactured as 200 milligrams as well as a 50 milligram capsule, and a 600 milligram tablet. I just share with the committee that the capsule can be opened and sprinkled on a small amount of food for younger children who cannot swallow a table, or in that case, an elderly person who can't swallow a tablet. The sponsor for this product is Bristo-Myers Squibb Pharmaceuticals.

The original approval was September 17, 1998 and that was for children 3 years and older. Then in May 2013 it was approved for pediatric patients 3 months of age to 3 years of age. It was those studies that prompted the current safety review that's being presented this morning. Those

submissions fulfill the PREA requirement for pediatric patients in the younger age group, 3 months and older.

A pediatric study was waived in children 0 to less than 3 months because this product would be ineffective and/or unsafe in this age group. I'll talk about that briefly a little bit later.

The next two slides I address the relevant safety labeling in this slide, Section 4, contraindications. Sustiva is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of this product. By hypersensitivity in parentheses, specifically Stevens-Johnson Syndrome, erythema multiforme, or toxic skin eruptions have been reported.

This is a listing of what appears in Warnings and Precautions, Section 5. The list continues to be long: drug interactions, resistance, co-administration with related products, psychiatric symptoms, nervous symptoms, embryo fetal toxicity, rash, which I'll speak to

more specifically, hepatotoxicity, convulsions, lipid elevations, immune reconstitution syndrome, and fat redistribution.

So the basis of approval for the younger patient is 3 months to 3 years old. It's supported by what you see on this slide. It was matching pharmacokinetics in the younger patients compared to adults, and that demonstrated antiviral activity as well as acceptable safety.

There were three open label studies evaluated and they included the PK safety and tolerability, as well as evaluation of antiviral activity of efavirenz in combination with other antivirals. So there were three studies, and the three sub-bullets speak to those open label studies. The first combination was efavirenz with didanosine and emtricitabine. That was in an anti-retro viral naïve and experience pediatric patients, and their ages for that particular study were 3 months up to 6 years of age.

The second open label study was efavirenz with didanosine and emtricitabine, a

slightly different population. That was in antiretroviral naïve pediatric patients, slightly different age group, 3 months up to 21 years of age. And then the third open label study was efavirenz in combination with nelfinavir and a nucleoside reverse transcriptase inhibitor in anti-retro viral naïve, and NRTI experience pediatric patients. Different age group, 3 months up to 16 years of age. And those were the supported studies for that labeling.

If you look at safety across these three open label studies, the adverse reactions were very similar to the adverse reactions observed in the adult trials. Except that incidents of rash was higher in pediatric patients. More specifically, 32 percent for all grades, regardless of causality, and more often a higher grade than in adults. I just listed below what that looked like. There were two pediatric patients with grade 3 rash, four pediatric patients with a grade 4 rash, and there were 5 pediatric patients who discontinued the study

based on rash.

The current pediatric labeling in Subsection 8.4, Pediatric use, reads as follow: The safety PK profile and biologic and immunologic responses to Sustiva were evaluated and antiretro viral naïve and experienced HIV 1 infected pediatric patients 3 months of age to 21 years of age in three open label studies. The use of Sustiva in patients younger than 3 months of age or less than 3.5 kilogram body weight is not recommended because safety PK and antiviral activity of Sustiva has not been evaluated in this age group. There is a risk of developing HIV resistance if Sustiva is under dosed.

This next slide speaks to the drug use. I just clarify, if you look at the top row, that's for Atripla, a combination antiviral product. If you look specifically at the pediatric drug use, 0 to 16, we (have 405 patients. There were 17 patients were our data shows that they were less than 11 months of age which is, of course, is not approved indication. If you compare that to the

bottom row, Sustiva specifically, the numbers are very similar, 0 to 16 years we have 326 patients.

This data is taken from the IMS data and looks at U.S. outpatient and retail pharmacies. It was collected between March 2013 and February 2016.

The adverse events, this data reported reports the number of adult and pediatric FDA adverse event reporting system that is our FAERS system. This was received since the pediatric labeling was included. If you look at that second line, pediatrics 0 to less than 17 years of age, there were 143 serious adverse events that were reported. We'll go into more detail on that in the next two slides.

So the serious adverse events, we have a total pediatric reports reviewed with serious, adverse events' outcomes was 143. The pediatric reports with the outcome of death is 26. Let me first direct your attention to the box on your left, in the lower left side, 0 reports that were excluded which totaled 116. We had duplicates of

31. We had transplacental exposure. There were 83 cases and that also included 10 deaths, and then there were two no individual patient was identified.

So let me direct your attention now to the bold box on your right, pediatric case series. We have a total of 27 and nine of those were pediatric deaths, so nine fatal cases and 18 non-fatal cases.

The summary of the pediatric fatal cases is as followed. We had immune reconstitution inflammatory syndrome in three pediatric patients, a 14 year old male, HIV infected with pulmonary mycobacterium avium-intracellular complex. A 12 year old male, HIV infection Kaposi sarcoma, who had been started on therapy for tuberculous, and an 8 year old girl, HIV infected with pulmonary tuberculosis. Antiretroviral drug resistance was documented in one patient, a 10 year old boy who'd been infected with HIV since about the age of 5.

Third category, HIV related opportunistic infection. There were three

patients. Two 16 year old girls and one 14 year old boy. And then unspecified infection in two patients, and they happen to be very young,

2 year old girl and a 3 month old girl. I just put the footer there in the subsequent

slide. Just be aware that unlabeled events will be reported different, and they will be underlined to help you clarify.

So the summary of all nonfatal adverse events reported for the pediatric patients, if you look to your left side, the labeled events there were a total of 11. Under Section 5, Warnings and Precautions, you see the details of the categories of the specific events. Under Section 6, Adverse reactions, there were a total of four events, and those are the conditions: peripheral neuropathy, ataxia, there were actually two patients, and pancreatitis, one patient.

In the next column to your right, the unlabeled events totaled three. Catatonia was reported in one pediatric patient, 16 year old, and there also were three adult patients who had

the same experience. Hypersensitivity and Fanconi syndrome were also reported. These are unlabeled, but they were potentially confounded, so keep in mind that clarification.

The disease-related events n=4. Actually, consider that to the left-hand column. That gives you a total of 18 patients.

So if we look across the summary of what's been presented with the new, three open label studies that supported the younger labeling, 3 months to 3 years of age this concludes the focused safety review for Sustiva. FDA is considering adding the term catatonia to labeling. There has been communication with the sponsor, and there appears to be agreement to revise the label.

FDA recommends ongoing routine pharmacovigilance, and at this point I would ask if the committee agrees?

DR. WHITE: Thank you for your presentation. We'd ask Dr. Towbin to join us because we have no representative on the committee in child and adolescent psychiatry. He's our past

chair here of the Pediatric Advisory Committee and is on the faculty at NIH in child and adolescent psychiatry.

Dr. Towbin, did you have any comments about the catatonia? I think that's what we were asking --

DR. TOWBIN: Yes. Absolutely.

DR. WHITE: -- your assistance with.

DR. TOWBIN: Yes. Thank you. Thank you for allowing me to join you this morning. I wish I could be there to see all your bright, smiling faces.

It's so hard to know what to make of a single case in the pediatric side of this. But in combination with those adult cases it did, for me, raise a concern, and so I guess the first thing to say is that I was quite pleased that FDA took this up with the sponsor and had talked about it. It's quite obvious that a number of factors may come into play since the appearance of neuropsychiatric symptoms with this drug. The mechanism for that is not at all clear.

So I guess the comments that I would make are that it certainly did, to me, seem reasonable to raise this as a treatable side effect that should have attention brought to it. And despite the, kind of, fragility of the data that we get from the FAERS system that it's still very reasonable to think about introducing this in label, in my own opinion.

DR. WHITE: Thank you for your comments. We're going to ask you to stay on line, if you don't mind, in case other members of the committee had questions or concerns. Any other comments? Concerns? Regarding --

DR. HOEHN: I had a question.

DR. WHITE: -- catatonia?

DR. HOEHN: Sorry. I had a question unrelated.

DR. WHITE: Identify yourself.

DR. HOEHN: Oh, sorry. Sarah Hoehn. I had a question unrelated to catatonia, but related to this presentation. Can I ask it?

So I just didn't know, I didn't see

anything that was per kilo dosaing, and the labeling says it goes down to 3.5 kilos in a baby 3 months of age. So I just didn't know if there was anything in the labeling that should address per kilo dosings if you're talking about giving a 200 milligram capsule to a 4 kilo baby. So my question was dosing related in labeling.

DR. WHITE: Would any of you like to address that for us?

DR. YANCEY: I'm going to defer to the colleagues from the Division of Antiviral Products. Can you introduce yourselves please?

DR. FARROW: James Farrow, Division of Antiviral Products, FDA. If you go into the labeling section of the Indications and Usage Dsoage Administration there should be the recommended dosage based on the weight. So even though that presentation just highlighted what the dose is, the actual dosing recommendation there's a -- if you look in Section 2 it goes by weight band 3.5 to 5 kilos, 5 to 7.5, et cetera. So it is specified how much to give based on their weight band.

DR. WHITE: Doctor, I can't see your name, sorry.

DR. HAVENS: Peter Havens.

DR. WHITE: Thank you.

DR. HAVENS: It might also be pointed out that the HAB U.S. HRSA guidelines for antiretroviral therapy don't actually recommend its use in children under age 3 without genetic testing because there's rapid metabolizers and slow metabolizers for whom there's a four-fold difference in dosing recommendations made by that guidelines committee.

The FDA recommended weight band dose is about halfway in between that. But some of the central nervous system side effects are actually related to blood concentrations of the drug. Given the genetic determinants of drug clearance, and therefore, drug concentration the guidelines committee has recommended a genetically determined dosing algorithm and does not routinely recommend it for children under age 3 years.

DR. WHITE: Any other thoughts or

comments? Dr. Shwayder?

DR. SHWAYDER: Well, since I'm the only dermatologist on the committee I just want to point out on page 44 where they list the various side effects that everything that's listed there could be considered eczema, with the exception of precancerous legions. Because eczema is a red itchy, sometimes bumpy, sometimes flat, and everything that list that list is red, itchy, sometimes bumpy, sometimes flat.

If it's important, we can develop a clear clinical guideline for side effects of drug, so you're not wrapping into this -- all the kids that come into my clinic for the last three years who have eczema or subdermal or all the other things that happen to little kids. That'd probably be a good idea and then you can elude out this data. That's all.

DR. WHITE: Thank you for your comment. Any other comments or concerns? Did the FDA want a recommendation regarding labeling?

DR. COPE: Yes.

DR. WHITE: So we should take a vote on --

DR. COPE: With discussions.

DR. WHITE: -- whether we should proceed with changing the label to add catatonia, is that...

DR. TOWBIN: Dr. White, I have a question about this.

DR. WHITE: Yes. Go ahead.

DR. TOWBIN: This is Dr. Towbin. I was wondering, in light of Dr. Havens' comments whether there would be anything in the labeling to suggest that the genetic assessment for rapid metabolizing would be indicated in children under 3 as part of the label?

DR. BELEW: So I can address the first question that was raised with regards --

DR. WHITE: Would you --

DR. BELEW: -- to labeling.

DR. WHITE: -- identify yourself, please.

DR. BELEW: Yodit Belew, Division of

Antiviral Products.

So we're currently in discussion with the sponsor with regards to labeling and the wording. So at this point we don't have specific wordings other than that we will be adding it on. But exactly how and where is under discussion with the sponsor.

DR. TOWBIN: So that was in regard to catatonia, I assume, but it leaves open the question about Dr. Havens' --

DR. BELEW: Right.

DR. TOWBIN: -- information, and I was wondering where that stands?

DR. BELEW: So for consideration to adding information into the label we would have to work with the sponsor, and we would have to have the actual data submitted by the sponsor to include such information into the label.

DR. TOWBIN: This is Dr. Towbin once again. Given the correlation between the data that Dr. Havens' suggested, and it sounds as if that was a consensus guideline, so it wasn't just

one person's one-off idea, but actually it does seem that there may be some data there. Although, this is not data that I know. And given the correlation between that data and these neuropsychiatric symptoms it would seem that just adding catatonia would be insufficient as a guideline for practitioners, and that a recommendation for obtaining that genetic assessment would be appropriate for this drug given the risks.

DR. HAVENS: This is Dr. Havens again. I think getting that into the label becomes really complicated because you then have to have a standard way to measure the specific genotypes which is not readily available. Which is why the committee, the guidelines committee, went to the general recommendation to not use it, and if you're going to then use it in the context of using blood concentrations to monitor where you are to avoid both resistance from low blood concentration or toxicity from a high concentration, which is a more practical way to

approach it.

I think the guidelines committee has members on it from the FDA and we work closely to bring together what's possible from the labeled indications and make that work in practice with guidelines that flow from the labeled indications. But may never get changed further because of impediments to changing the label which are it's a pretty high bar. In this case, especially if you need a blood test prior to choosing a dose.

DR. TOWBIN: This is Dr. Towbin, again. Dr. Havens, thank you so much. I actually -- there's so much wisdom in your comments there, and so I appreciate them very much.

Would there be a way in which the recommendation for following blood levels and the concern about rapid metabolizers being at higher risk be something that could be considered as part of the labeling then?

DR. HAVENS: That's an FDA question.

DR. TOWBIN: Yes, it is.

DR. WHITE: Dr. Nelson?

DR. NELSON: Skip Nelson, OPT. I won't address that directly, but this general issue of the need for genetic testing around issues of rapid metabolizers, slow metabolizers and so on and so forth is an important topic. It relates to a number of other different drugs, but I just call the attention to the committee that the extent that you put that in the label you end up, A, you need an in vitro diagnostic device which goes to the question of whether or not a genetic test is, in fact, available in the commercial setting as opposed to the research setting.

DR. TOWBIN: Mm-hmm.

DR. NELSON: Or whether there are other approaches to being able to determine whether someone is or is not a rapid or slow metabolizer and so on and so forth. So that becomes an issue, and you then link that device to the use of the drug. So there are some interesting, albeit it important, complex questions around how drugs and devices would then interact around the labeling.

It's not unusual for FDA to try to take

a middle position where you wouldn't require the use of a particular device, particularly if it's not available commercially. But might try to work out some process by which, you know, the recommendations of the committee to dose appropriately if you're a rapid or slow metabolizer could be sorted out clinically.

So it's a more general issue, and particularly, as we go towards precision medicine where dosing of different drugs are related to slow and rapid metabolizers it's not unique to this particular product.

DR. TOWBIN: Thank you for that, Dr. Nelson. I do have a follow up question which is since this is not a drug that I use in any routine way, is monitoring blood levels standard practice?

DR. HAVENS: No, it's not.

DR. TOWBIN: So would there be room to suggest that and at least raise practitioners' awareness that the experience for rapid metabolizers could put them at higher risk?

DR. HAVENS: Yes. Therapeutic drug

monitoring is recommended by the pediatric guidelines for the United States which form the basis of many other guidelines, and is used by many of the drug compendia people to inform what they put into readily available online resources in combination with the labeled information put out by the FDA.

DR. TOWBIN: So we've got --

DR. HAVENS: That was Havens again.

DR. WHITE: Dr. Shwayder?

DR. SHWAYDER: Tor Shwayder. So I'm looking at slide 14. There's almost 400 kids and they had the one case of the catatonia. I need to ask, since I don't do this, can you get catatonia from having HIV? Can you get catatonia from having a high fever? Can you get catatonia from any of the other drugs that they might be on to treat their HIV?

If we link this to catatonia then it stinks. It stinks. And are we -- it behooves us to know whether it was cause and effect.

DR. WHITE: Anyone from the FDA like to

comment?

DR. BELEW: Yodit Belew, DADP. Thank you for that comment. So we did struggle with that specific case, and I believe you guys got the narrative for the case. Paula can get into the details, but there are some limitations into the -- that single report with regards to weight loss. Maybe that patient was overdosed for a little bit when he got that symptom, and then when they reverted back to his original dose it seems like the symptoms went away.

But given that there were three other cases in the adult population that were identified that was one of the reasons to put it in the labeling. But stepping back, efavirenz is known to have neuropsychiatric adverse events. If you look in the warning and precaution section the psychiatric events, it's a laundry list of a number of events.

So looking at it from that end it's not unreasonable to think other psychiatric events could occur. So that was sort of the thinking

behind why to include it in the label.

DR. TOWBIN: This is Dr. Towbin. Just to add a comment here. So the thing that would be a bit special about catatonia, as FDA has pointed out, is that one might not be looking for that being linked to the drug. Even though these other neuropsychiatric symptoms are listed. I think FDA has it right on the second issue with is the intervention for catatonia might be very different than the intervention for some of these other neuropsychiatric symptoms, and so adding it to this section of the labeling actually made good sense.

But I fully agree that based on one case one might not to want to take these steps. But when you see the experience with rechallenging the patient, causing the symptoms once again, and you add it to what the adult experience has been it would seem a safe step to add this. I also think Dr. Haven’s comments, once again, are relevant here. That the genetic predisposition of some individuals to rapidly metabolize this drug

could be linked to these neuropsychiatric symptoms. Therefore, one wouldn't expect to necessarily see a great number of individuals with this problem, but that could explain why some do.

MS. GISH: As far as causality, there were three adult patients --

DR. WHITE: Could you identify yourself please?

MS. GISH: I'm sorry. I'm Paula Gish. I'm an OSE safety evaluator. There were three adult cases with a temporal relationship and all of them had a positive de- challenge, and two of those people had high drug levels of efavirenz, 6 to 25 times the normal level. One had a positive re-challenge, so that's where the causality came in.

DR. WHITE: If I might summarize. Dr. Cnaan?

DR. CNAAN: One more small comment. That is that the prevalence of catatonia in the U.S. is 90,000 cases a year from everything. And so if in the context of these short, relatively

short clinical trials and these small number of people, relatively, we ended up with four cases, three adults and one pediatric that further supports that there is something happening here.

DR. WHITE: So if I might summarize. We're going to vote yes if we feel that we should support consideration of addition of catatonia to the labeling for this drug. Can we start -- I guess we're going to use the voting thing here. Yes would be to support. No would be that we don't feel it's necessary. If you want to press yes or no please?

DR. NELSON: Michael, let me just clarify.

DR. WHITE: I'm sorry.

DR. NELSON: So we're going to have two votes.

DR. WHITE: We're going to have two votes, yes.

DR. NELSON: I just want to be clear. But the question -- I've heard some discussion around levels and that sort of thing. So the

catatonia is one issue, but the discussion of therapeutic drug monitoring, is that something that the committee wants to opine on as well?

DR. TOWBIN: Dr. Towbin would like that to be opined on. Thank you, Dr. Nelson.

DR. WHITE: I was thinking about conserving that for comments going around the table, but if you think we should --

DR. NELSON: Well, I think --

DR. WHITE: -- consider that as a second round.

DR. NELSON: -- comments around the table don't have the same cache as the committee's opinion on whether therapeutic drug monitoring or attention to levels or whatever. So, you know, I would, you know, if you want to go around about catatonia that's fine, and before you do the other have some discussion about whether you think that ought to --

DR. WHITE: Okay.

DR. NELSON: -- be a recommendation to committee or not. Because a discussion doesn't

carry much cache as opposed to a vote.

DR. WHITE: Alright. Let -- go ahead.

DR. HAVENS: What do you mean a recommendation about therapeutic drug monitoring? Peter Havens.

DR. NELSON: Well, to back up. Whether or not the label ought to include something along the lines of what you've articulated is the recommendation around practice guidelines about the importance of monitoring, vis-à-vis, rapid metabolizers, and the potential link to the catatonia which we're adding to the label.

Whether that's something you as a practitioner think would be helpful in the label itself as opposed to in the guidelines? I'm just following up on your comments about what the guidelines currently say.

DR. HAVENS: Peter Havens. So then the recommendation or so we might make a statement that FDA would discuss with the sponsor the potential for putting in a recommendation for therapeutic drug monitoring for smaller children.

DR. NELSON: That's the question. Whether you think you could articulate that in a way that is votable.

DR. WHITE: Okay. I think most of us have pressed the -- can we defer for a moment and vote on the first issue which was to support the labeling? Since I think most of us have pushed a button. Some of us have not, and then we'll open discussion for Dr. Nelson's consideration.

Have we completed the voting on the first suggestion? Okay. And do we have that vote? It looks as if all have voted in favor of suggesting a considering of adding catatonia to the label. We still have to go around the table. Can we start with -- can't read your name, sorry.

DR. FISCHER: It's Gwen Fischer. I concur with the addition to the labeling.

DR. MOON: Mark Moon, I concur.

DR. SAVEL: Wael Savel. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. TURRER: Christy Turer. I concur.

DR. SHWAYDER: Tor Shwayder. I concur.

DR. CNAAN: Avital Cnaan. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. WADE: Kelly Wade. I concur.

DR. ANNE: Premchand Anne. I concur.

DR. WHITE: Thank you all. Now, the question --

DR. TOWBIN: Dr. White?

DR. WHITE: Yes?

DR. TOWBIN: This is Dr. Towbin --

DR. WHITE: Yes, doctor?

DR. TOWBIN: -- and I vote yes.

DR. WHITE: Thank you. I'd almost forgotten. Thank you for your vote and your --

DR. TOWBIN: You know, out of sight is out of mind.

DR. WHITE: Well, not out of mind, but

so the question has been raised about whether we should make a recommendation or not regarding drug level acquisition to guide treatment. I guess we would do this for the pediatric population only since we don't really have any sway in the adult world.

Is there an opinion from any of the committee members regarding whether we should put that proposal forth or not? We have two people on the end. I'm sorry, help me with names.

DR. HOEHN: Sarah Hoehn. I had a question related to that. DR. Havens mentioned that HRSA doesn't recommend using it in the first three years of life, so I didn't know if that should be linked to the question about consider therapeutic monitoring -- if you should especially consider therapeutic blood levels under 3 years of age.

I just didn't know if we should have any connection to that based on the follow up. To connect the labeling to what Dr. Havens said the consensus guidelines are.

DR. HAVENS: This is Dr. Havens. The pediatric guidelines state that therapeutic drug monitoring is recommended with an efavirenz concentration measured two weeks after initiation. Some experts would also measure at three years when making the dose adjustment. So that's what the HRS guidelines recommend.

DR. CUNNINGHAM: Thank you. Melody Cunningham. So if in the adults the levels were 6 to 25 times higher than anticipated then it seems to me, it's almost a no-brainer about whether we should make that recommendation for monitoring, and perhaps some of those other side effects that are already labeled may be related to drug levels and the, you know, rapid metabolizers.

DR. WHITE: Dr. Havens, again.

DR. HAVENS: Well, no. Remember what Dr. Nelson said, that as soon as you make a recommendation to link a test with drug usage it gets way more complicated because you have to approve the test. Not everybody has availability of the test. People won't pay for the test. And

so usage becomes dramatically more complex.

DR. WHITE: If I might summarize in response to Dr. Nelson. It seems as if this particular question we weren't provided the information we probably need to make a recommendation for drug level monitoring. But it might be a question that we could ask the FDA to investigate and bring back to committee at the next meeting for consideration. With more information regarding whether levels are indicated or helpful.

Are there other opinions, maybe, regarding that? Dr. Wade?

DR. WADE: Kelly Wade. Before, I think, we're going to turn it to the expert representative from the FDA, I would just ask if you can help clarify or remind us the information that's already in the label under clinical pharmacology or clinical pharmacokinetics, and how much this discussion of variation and metabolism and genetic influence of drug metabolism may already be in the label, just in another section?

Can you just remind us what information about this topic is already in the label in a different section?

DR. VISWANATHAN: Just give us a moment. This label is very extensive, and we are just reviewing it before we comment.

DR. BELEW: While Prabha is looking at the label I also just want to make a comment about the discussion at hand with regard to therapeutic drug monitoring. So if we assume that efavirenz, and it has been demonstrated that it does have neuropsychiatric adverse events, demonstrated both in adults and pediatrics. We can't divorce the two populations and recommend drug therapeutic for pediatrics only. If that's the path that we're taking then would have to be all population and not just pediatric patients.

The other comment that I want to make is that efavirenz has been on market since the 90s, so it's a pretty mature drug, and it's been used as first-line regime in adults for years. So the other question is for those who are already taking

the drug, even if they may or may not have psychiatric adverse events, would they then have to have therapeutic drug monitoring even if they have been on the drug for years?

So there are a lot of questions and I definitely agree that the data should be reviewed and presented before it's voted on.

DR. WHITE: Dr. Cunningham?

DR. CUNNINGHAM: Melody Cunningham. I just wanted to clarify. I wasn't suggesting genetic testing which is clear is not readily available, but therapeutic drug level monitoring.

DR. WHITE: Can I attempt to summarize and maybe bring a question that we can vote? Yes, go ahead.

DR. BELEW: If I could just --

DR. WHITE: FDA.

DR. BELEW: FDA. Make an additional comment related to what was just said. So if we're not doing genetic testing we're basically monitoring blood levels. Then patients are already on the drug if you're doing, so how does

the testing or adding that additional information change practice management?

Because if you're already on the drug you can also wait to see if they have adverse events. Then decide to switch regime instead of just doing blood levels.

DR. WHITE: Dr. Havens, would you like to comment on that part of it?

DR. HAVENS: The biggest effect of the genetic differences seems to be in the youngest children under age 3. I think that making a general recommendation for monitoring plasma concentrations, as FDA points out, would dramatically change what many people do already.

It should be noted that in many studies up to 20 percent of people stop efavirenz because of drug side effects. They're not usually severe. They just can't concentrate or they have bad dreams. So the clinical monitoring is usually taken as a reasonable approach to this problem.

DR. WHITE: Dr. Cunningham?

DR. CUNNINGHAM: Sure. Melody

Cunningham. So the way that I see that it might change things therapeutically is if the patient has a side effect you check the levels, and if they're high they may stay on this drug that's effective for them. But the dose might be diminished and mitigate their side effects. So that's how I see it might be clinically relevant.

DR. BELEW: Then you run the risk of development of resistance, so you wouldn't actually decrease the dose if they're not tolerating the drug because of adverse events. You would just discontinue it.

DR. WHITE: Dr. Havens?

DR. HAVENS: So, first of all, yes, to the first question of what you would do if you had somebody who had a side effect with a documented high plasma concentration. You could decrease the dose. I would argue that this is the place where guidelines are better than changing the label.

That there is a place for the collaboration of FDA and guidelines writing committees. We've already referred to this when

we talked about the vaccines where FDA had recommended or had approved it down to age 2 months, and then the question came up, what did CDC and ACIP recommend. And in a same kind of way, I think that FDA makes labeled recommendations that are appropriate and reasonable, and then guidelines committees can take them on and apply them. In your case, to a practice activity.

Then in response to the FDA perspective. Right, if you were going to change based just on a clinical adverse event you wouldn't decrease the dose because you wouldn't know what the right dose was to use. But, in fact, we use efavirenz plasma concentrations like verapamil plasma concentrations, very closely in our pediatric practice so that we make sure we have the right dose and find a wide variability in dose that is needed to give appropriate therapeutic drug concentrations.

But I think that that really is the purview of a guidelines for clinical practice

rather than a change in the FDA label which has a completely different level of difficulty and meaning in the public forum.

DR. BELEW: Thank you, Dr. Havens. To add to that, while you may adjust the dose based on guidance recommendation, for us to recommend changing a dose we have to have a clinical trial that has shown a lower dose has been shown to be effective. We cannot just recommend a lower dose without having a clinical trial.

And particular, for adults or pediatrics, for that matter. So if we don't have an alternative dose already recommended in the label that would have to be a new study demonstrating an effective therapy from a lower dose.

DR. TOWBIN: This is Dr. Towbin, I just wanted to make one comment. I'm very grateful to Dr. Havens for the comments that he's making. I would concur with his perspective that using the label to establish practice really can be very cumbersome.

But I think the other side is we still have this question outstanding about whether the label includes some of the concerns about rapid metabolizers, as Dr. Cunningham has so nicely laid out. And so I think, for me, the question would be whether there could be a value for practitioners and patients of making clear that there is a risk for rapid metabolizers of increased ill effects, neuropsychiatric effects in particular.

That might actually guide things like family history or other kinds of experiences with other agents in the decisions about using these agents. Since we know rapid metabolizers may be individuals who've had adverse events to other drugs.

DR. WHITE: Dr. Hausman?

DR. HAUSMAN: Hi. This is Ethan Hausman from Pediatric and Maternal Health. With respect to the comments that just came up, one of the difficulties and shortcomings with making those recommendations without actually having the

hard-core data in the beginning is one can infer from the FAERS database, and even from practice guidelines which may be supported by class A, B, or C evidence that there might be a link. But it makes it very difficult to actually inform the label constructively about therapeutic drug monitoring, particularly for adverse events, when we don't have the support of good, quality data.

DR. WHITE: Dr. Nelson?

DR. NELSON: If I may, just a couple of comments. You know, part of my interest in this conversation is I gave a talk just yesterday to the T-32 NICHD/NIGMS clinical pharmacology training program. And heard a very interesting presentation, I won't mention the drug, by Steve Leeder where he presented some data, and, Ken, you'd be interested about ADHD and a particular drug that may or may not be working well because of differences in slow, rapid, fast metabolizers and so on and so forth.

So this is a general issue that impacts in pediatrics. I guess I might be so bold as to

suggest I don't hear a sort of clear consensus emerging from this conversation, and I just wonder if there would be a way at some point in the future if we can, as we are trying to get important things on the agenda for the PAC, maybe have a broader discussion of the role of therapeutic drug monitoring, genetic testing for rapid and slow metabolizers to six or whatever.

DR. TOWBIN: Mm-hmm.

DR. HAVENS: As a more general conversation. Because this is not unique to this product and it's a very, you know, complex issue involving both clinical trials and future diagnostic devices and so on and so forth. Impact on access, etcetera. So an important topic.

I would hesitate to have a premature vote on something that is, as Peter points out, fairly complex in a relationship between the label of practice guidelines, understand of genomics, et cetera. So, you know, and maybe we could try to think down the line of a broader conversation about that. I mean, this is one example, but

there are other examples that one could bring to bear on that topic.

DR. WHITE: I'm going to try to summarize this. Yes, Dr. Moon or not Dr. Moon. Go ahead, Dr. Jones.

DR. JONES: I just had a comment, Bridgette Jones. On those same lines, I think this is a really complicated issue and I think, you know, maybe there are some assumptions being made that genetic variation is playing a role in alternative exposures in its relationship to the catatonia or other side effects. But other things also should be considered like drug interactions. Maybe these patients were on several other drugs that could interact with the metabolism of the drug and effect exposures and also, the impact of ontogeny and age.

The fact that some children, when they're younger, some of the enzymes may work differently related to age. So I think there's a lot of other factors that should be considered besides just genetics.

DR. WHITE: I'm going to try to summarize this and help me, Dr. Nelson, you might help me clarify this. It appears that there are some concerns about the potential for drug levels to be interacting with the side effects that we've seen.

So I think what I'd like to do is ask the FDA to review the data on drug levels and genetic variance in this particular drug and come back to us with a recommendation for whether to proceed with consideration of changes in the label related to any potential observations that you make.

Dr. Nelson, does that clarify it well enough?

DR. NELSON: Well, that's fine. But I guess, in my mind, Judy and I can think downstream about topics. I mean, for example, you may remember at the last meeting we said let's talk about neuroapoptosis in a few years when we have clinical trial data. I mean, this may be something that merits a broader discussions. Not

focused on this particular drug but, you know, the drug, Ken, that was presented yesterday afternoon was for ADHD. So, I mean, it's a broader topic.

So we could bring in a number of different examples and have a broader discussion of this issue as the emphasis on precision medicine evolves. That's what I'm thinking. I mean, that's a more specific drug related question which we can certainly fold into it. When we could carve out time for that, we'd have to look at our schedule. But that's sort of what I was thinking. You know, work with the people within the FDA about how useful that is, but really take attention off of this product, per say, and broaden it to say how do we approach that?

Particularly in pediatrics where those genomic interactions may have more of an impact as you get to lower weights, and so on and so forth. So that was the idea. I don't think we necessarily need a vote on that. Maybe a sense of the committee about whether that's a worthwhile direction to go.

DR. WHITE: Well, I think we've raised the question in this specific drugs in a number of peoples' minds, so I think we have to -- maybe we don't have to, but I would feel like we should probably make a recommendation or not that this specific drug be considered and the data brought back to us.

And then your recommendation is for a broader educational perspective and I think --

DR. NELSON: Well, I guess I'm not sure what data we have and that's --

DR. WHITE: And we may have none.

DR. NELSON: Yeah.

DR. WHITE: We may have none.

DR. NELSON: Look at the data.

DR. WHITE: But that's okay. If that's the information that comes back is that there is no data then it's a quick discussion.

DR. BELEW: Yodit Belew.

DR. WHITE: Go ahead.

DR. BELEW: I just want to mention a question was brought up about the label and what's

included in the clinical pharmacology section. It does talk about its metabolism and how it's CYP inducer. So you can imagine if it's a CYP involvement how different people would metabolize it and who would have a higher level versus not.

DR. WHITE: I'm looking for guidance. This is new to me. I think we have to wrap this up, so a vote.

DR. NELSON: To me a vote carries weight when you have a labeling recommendation, and the reason for that is because this committee is the place where differences of opinion between divisions and the sponsor are adjudicated although we've never had that happen.

So in the absence of a clear -- I mean, you know, in the --

UNIDENTIFIED MALE: There's no consensus.

DR. NELSON: In the absence of a clear labeling recommendation I'm not sure, necessarily, we need a vote to say this is an important topic to bring back to committee. I think it's an

important topic to bring back to the committee. I don't know if that would be in 6 months. I don't know if that would be in 12 months.

We would have to line up some drugs. Line up the clinical pharmacologists, get the pharmacogenomics people involved, et cetera, and plan that which would probably put it out to, at best, a year from now. So I, you know, I think our office can work on trying to put that together independent of a vote of the committee, frankly.

DR. WHITE: Dr. Havens?

DR. HAVENS: I'm very supportive of that. I'm feeling a little guilty that I've opened up a can of worms here. But I do think that this is part of a much broader discussion and how to bring labeled indications to bear on clinical practice, and what's the most effective way to do that in a rapidly changing environment, and whether or not it's genetics or drug concentrations that are really the issue.

As we hard earlier, this is a very important issue that changes with patient age

because of the maturation of different enzymes and the relative contribution of liver and body surface area, blah, blah. So it's a very complicated issue that, I think, bringing it together with a variety of different drugs really would be very useful.

I only hope that you get to it before I retire from the committee.

DR. TOWBIN: This is Dr. Towbin just coming in. So. Dr. Havens, I won't allow you to take responsibility for opening the Pandora's Box single handedly. I assisted you in that or I may have been the one with the crow bar and you were just there with the information.

But I do think that Dr. Nelson's suggestion is an excellent suggestion. I think this is a really good role. My view of the PAC is that this is a really good role for the PAC to play with FDA, to think about these broader issues.

I guess, my issue about the label is that I think the label can be a way of informing

practitioners about risks and concerns. And so, unfortunately, I don't have the label in front of me, but the question that I would raise, not for a vote, but just to kind of put out there is whether the language about metabolism is strong enough or clear enough so that people would be aware that that's a thing that they should be thinking about. And that blood level monitoring would be a consideration in someone who is presenting, particularly, with neuropsychiatric side effects and as the kind of first line.

I think the comment about, I think it was Dr. Jones, that said that, you know, there are other drugs on board. There are drug interactions. And yet, a blood level would be really the best way to determine that someone really has much too much on board and that something needs to be done about that.

DR. WHITE: We have comments from the FDA.

DR. BELEW: Yes, Yodit Belew. If you look in the Warning and Precaution section the

first warning, 5.1, is drug interactions, and it clearly states efavirenz plasma concentration may be altered by substrates, inhibitors, or inductors of CYP3A. Likewise, efavirenz may alter plasma concentration of other drugs metabolized by CYP3A. So that is the first warning with regards to the potential changes and the concentration of efavirenz.

DR. TOWBIN: Thank you for that.

DR. WHITE: So I'm going to try one more time. I am going to bring this to vote because I think that's the only way with all the comments we can resolve it. I would like to suggest that the FDA, we're going to vote to request that the FDA come back to us with information regarding use of label of -- pardon me, drug levels and possible genetic variation.

Did I make that clear enough for a vote? So a yes vote will be --

DR. HOEHN: Can I just clarify?

DR. WHITE: Sure.

DR. HOEHN: Is that for this drug in particular or for --

DR. WHITE: For this drug in --

DR. HOEHN: -- or for Dr. Nelson's comment of a --

DR. WHITE: No.

DR. HOEHN: -- broader discussion?

DR. WHITE: No. For this drug in particular I think the broader educational objectives can be met without a recommendation. Is that correct, Dr. Nelson?

DR. NELSON: Whether I would characterize it as educational, I think, would be the open question. But, I mean, if you think you want to see specifically about this drug that's fine, but it's, you know, but.

DR. WHITE: I think we need to vote on it. I'm not sure everyone will agree.

DR. NELSON: I don't think we do. I mean, I haven't heard a clear recommendation that's come out from that. So, I mean, if you

want to -- so to just say you'd like the data back, if you want to see the data at some point then that's fine. But, you know, it's unclear what you would do with that data at this point in time, so I don't think you need a vote, necessarily, to resolve that because there's no question that I think it --

DR. WHITE: Okay. Dr. Cnaan?

DR. CNAAN: I think what we're hearing is that there's enough around the committee that we would like to see what the data are, and also any association with side effects. Maybe there is none between the levels in side effects. Maybe there is. But I think we're in a position where none of us feel comfortable making any recommendation about labeling, but we just want to know a little more. That's what I'm hearing.

DR. WHITE: I'm sorry, I --

DR. HOEHN: Sarah Hoehn. I have another question. I didn't know based on the language of the labeling if there could be recommendation to say, consider therapeutic drug monitoring when

toxicity. Because they talk about seeking immediate medical evaluation. If you could just add four words to say consider checking a level if they develop toxicity.

DR. BELEW: Yodit Belew. I think from clinical practice if someone is having side effects, regardless of what the drug level is, you would manage that patient according to symptoms. So you'll either discontinue regardless of the drug level or continue if the side effect is not severe.

DR. WHITE: Okay. I'm sort of caught between what Dr. Nelson is asking and my feeling from the committee that the committee's uncomfortable with the information that we have. The only way I can think to get through this is to call a vote which would be we would like the FDA to come back to us with a review of the role of drug levels in genetic testing for this specific drug, and that would be the vote. Yes, we would like them to come back. No, we will like we have the information we need and we are comfortable

with the FDA continuing routine monitoring.

That question will come up later because we have to vote on that specifically. Can we vote now? Is the vote complete, and Dr. Towbin?

DR. TOWBIN: Dr. Towbin votes no.

DR. WHITE: No, okay. Is the vote complete? Okay. It looks like yes, the committee would like you to come back with some information regarding the potential use of drug levels and genetic testing for this specific drug.

Now, the question that was raised by the FDA initially was return to routine monitoring, I believe?

DR. NELSON: You need to go around the room.

DR. WHITE: Oh, I'm sorry. Yes, thank you for reminding me. Do we start down there? We'll start down there.

DR. FISCHER: It's Gwen Fischer. I voted no based on the reasons that Dr. Havens brought up, but I would be interested in hearing a more general conversation about this in the

future.

DR. MOON: Yeah, Mark Moon. I voted no. I mean, we could do this for any drug.

DR. SAVEL: Wael Savel. I voted no. I agree with Dr. Nelson and with Dr. Moon that we can do this for many other drugs, and I can think of at least ten drugs I use on a daily basis on my patients that could benefit from drug monitoring and/or genetic testing before prescribing those medications.

I think the issue here is age dependence and whether that should be included or not. So if patients under 3, if they are more susceptible to toxicity because they're rapid or slow metabolizers. I think that's a separate issue from the general consensus here.

I do think that this is an important topic that we should discuss, in general, but not necessarily pertaining to this specific drug. But in general, I think we could definitely use more information about it.

DR. HAVENS: Havens, no.

DR. TURER: Turer. I had voted yes, although I do concur with your statement. It's more about the broader conversation and not so much about the specific drug, so if that is the question then I would change my vote to a no.

DR. SHWAYDER: Shwayder. I voted yes.

DR. CNAAN: Avital Cnaan. I voted yes. I feel that regardless of the broader discussion, which is definitely great, whatever slim information exists on this one it would be a good idea to see it in about a year and see if we have anything or it is so slim and thin that we cannot for this one. Regardless of the general conversation.

DR. CATALETTO: Mary Cataletto. I voted yes.

DR. CAMPBELL: This is Jeff Campbell. I actually obtained.

DR. CUNNINGHAM: Melody Cunningham. I voted yes. Although as I think of the comments at the other end of the table, I think if I thought about whether to do this or to look at the broader

view I think that the broader view is more important, and it probably does relate to many drugs. So I would actually change my vote to no.

DR. HOEHN: Sarah Hoehn. I voted yes, but I would agree with the other half of the table and change my vote to no.

DR. DRACKER: Bob Dracker. I would vote no. I think it will interfere with use of the drug.

DR. WADE: Kelly Wade. I voted yes in case this is a unique scenario in the lower age dependence children. But I support the more general conversation of the rule of the label information in this domain.

DR. ANNE: Premchand Anne. Yes.

DR. WHITE: After all the vote changes, and the fact that I actually pressed the button and wasn't supposed to I think the vote is no. There's a strong consensus that future programs considering this, whether educational or informative, I'm not sure how to characterize it would be.

DR. TOWBIN: Dr. White, I just had --

DR. WHITE: Yes. I'm sorry, Dr. Towbin. I keep forgetting. I apologize.

DR. TOWBIN: Oh, no, no. It's fine. No offense taken. So my vote was no. I do think that it could be productive, really on both sides, that is for FDA to have the PAC's advice on how to think about these issues in the broader context, and also for the PAC to hear from FDA. How they think about it and would understand an approach to this issue. I think that actually could be a constructive conversation and useful. But I don't think it should be about this specific drug and that was my rationale for voting now.

DR. WHITE: Thank you, all, for your comments. The final vote that we have is FDA recommends ongoing routine pharmacovigilance for this drug, and the question is does the committee concur. Can we call that vote? We need the lights please.

And the vote is unanimous in favor of routine pharmacovigilance.

DR. TOWBIN: And that includes Dr. Towbin who concurs.

DR. WHITE: Thank you, Dr. Towbin. How many times can I forget you're there today?

DR. TOWBIN: It's fine. You know what? When we see each other it's always a warm occasion.

DR. WHITE: Yes. We need a picture of you on the screen here, just so I know that you're there.

DR. TOWBIN: No. Please don't scare the participants like that.

DR. WHITE: We'd like to thank you for your participation today and your insightful comments.

DR. NELSON: We still need to go around the room.

DR. WHITE: Thank you, Dr. Nelson. I was not prepared for this at all.

DR. ANNE: Premchand Anne. Yes.

DR. WADE: Kelly Wade. Yes.

DR. DRACKER: Bob Dracker. Yes.

DR. HOEHN: Sarah Hoehn. Yes.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CNAAN: Avital Cnaan. Yes.

DR. SHWAYDER: Shwayder. Yes.

DR. TURER: Turer. Yes

DR. HAVENS: Peter Havens. I concur.

DR. SAVEL: Wael Savel. I concur.

DR. MOON: Mark Moon. I concur.

DR. FISCHER: Gwen Fischer. I concur.

DR. WHITE: Dr. Towbin, I think you've already expressed your comments. Thank you very much for your participation today.

DR. TOWBIN: Thank you very much. I concur as well.

DR. WHITE: And thank the committee for your patience in my taking charge of the meeting.

DR. TOWBIN: It's all good. Thank you very much for letting me join you for this

discussion, and to participate in this important work. Bye, for now.

DR. WHITE: Dr. Hudak has pulled his chair back to the table. You all will be happy for that.

DR. HUDAK: Thank you, Dr. White. Well done. I just might take the chair's prerogative here not to speak about Sustiva, but to point out that the FDA website actually has a section dealing with the drugs that have label information on pharmacogenomics. At my last check back in April I think there were 100 drugs that have information on different metabolism and different pharmacogenomics, so I think this is a relevant subject to entertain on a more broad basis.

So we will get back with the program. We were a little off schedule. So I'll have to cogitate on what we do about a break, but we will proceed with the next presentation which is on Topamax. Here to do that is Dr. Khurana.

UNIDENTIFIED FEMALE: We have someone new to the table.

DR. HUDAK: Someone new to the table. We have someone new to the table.

DR. LEVIN: Hi. Bob Levin, FDA, Pharmacovigilance,OSE.

DR. HUDAK: Very good. All right. And, Dr. Khurana. Thank you.

DR. KHURANA: Thank you. Good morning. I'll be presenting the pediatric focus safety review today for Topamax. This is the outline which I'll be following.

So first, by way of background, Topamax is an antiepileptic drug containing topiramate as the sole active ingredient. It's approved as oral tables and oral sprinkle capsules. Topamax was first approved in the U.S. in 1996 as an adjunct to treat partial onset seizures, initially only in adults, but is now currently approved at both mono therapy and adjunctive therapy for several different seizure types in both adults and pediatric patients down to 2 years of age.

Topamax's March 2014 approval for extension of the migraine headache prophylaxis

indication to adolescence prompted this pediatric focus safety review.

The next few slides highlight relevant safety information in Topamax labeling. Current labeling does not include a boxed warning or contraindications for use in adults or pediatric patients. The warnings and precautions section contain 16 subsections which are listed over the next two slides, with prominence given to the possibility of visual complications and adverse neuropsychiatric events including suicidal behavior and ideation.

The efficacy of Topamax as a migraine prophylaxis in adolescents was established in a multicenter, randomized, double blind, parallel group trial in 103 patients 12 to 17 years of age with episodic migraine headaches with or without aura. The patients were randomized to receive Topamax 50 milligrams daily, 100 milligrams daily or placebo.

Trial results showed the superiority of the 100 milligram Topamax dose over placebo for

the primary efficacy endpoint. The long term safety of Topamax as migraine prophylaxis in adolescence was based on the pivotal efficacy trial. As well as from a flexible dose placebo control study in a broader pediatric age range, and from the open label extension phases of three studies of migraine prophylaxis, primarily in adults, that collectively included

adolescents. Most of the adverse reactions in the adolescent

migraine patients was similar to the known safety profile of Topamax in adults and pediatric patients treated for other indications. Newly recognize adverse reactions are highlighted in bold on this slide, and were incorporated into labeling with approval of the migraine prophylaxis indication in adolescents.

Both pediatric trials were summarized in the pediatric use subsection with cross references to the relevant sections in Topamax labeling. This information is detailed over the next few slides. Trial information was included throughout

labeling since the product is approved in pediatric patients.

Now let's look at the use of topiramate. This table displays the total number of pediatric patients 0 to 18

years of age who received a dispensed prescription for topiramate from U.S. outpatient retail pharmacies from March 1, 2014 to February 29, 2016. Pediatric patients 0 through 17 years of age accounted for approximately 7 percent of topiramate use during this time period.

Now we'll look at the pediatric-focused adverse events. We identified 121 U.S. pediatric reports with topiramate reporting a serious outcome from March 1, 2014 which was the date of the last pediatric labeling change for Topamax to February 29, 2016. After adjudication, 45 reports were excluded for the reasons listed on the bottom left of this slide, resulting in the selection of 77 domestic cases of topiramate use reporting a serious outcome which were the basis for this pediatric-focused safety review.

These included three fatal cases and 73 non-fatal cases which described a total of 190 drug event combinations. A drug event combination is a drug and adverse event combination reported in at least one case in the database. Cases may have more than one drug event combination. For purposes of this review, we focused on deaths, and serious unlabeled drug event combinations.

Three patients died. The reported death was associated with a respiratory infection in one case, and with a seizure in another case. The cause of death in both cases was likely disease related. Concomitant use of other anti-epileptic drugs in these two cases could have confounded the assessment.

The third case reported cardiac and respiratory arrest due to a completed suicide with ingestion of an unknown amount of topiramate. This case did not contain enough details for assessment.

The majority of the serious reported drug event combinations were consistent with the

known risks described in Topamax labeling, and no apparent increased severity was observed in these cases. We identified six cases reporting seven serious, unlabeled drug event combinations of interest with topiramate use in the pediatric population. Including the fatal case of cardiac and respiratory arrest from a completed suicide that was previously discussed.

The adverse reaction section of Topamax labeling currently includes anorexia and weight decrease. But we identified three cases which reported the eating disorders of anorexia nervosa and bulimia nervosa in adolescent females who were taking Topamax to treat migraine. All three adolescents reported either a family history of eating disorders, a personal medical history of anorexia nervosa or major depressive disorder. All of which are risk factors for anorexia nervosa or bulimia.

One case reported acute kidney injury and hypovolemic shock secondary to acute hepatic failure in an 11

year old boy who had been receiving topiramate for epilepsy for 10 years prior to his presentation. His liver function and associated laboratory abnormalities improved with discontinuation of topiramate. A liver biopsy was reportedly consistent with drug-induced liver injury.

Hepatic failure is listed in the post-marketing adverse reactions section of labeling. However, to date, FDA has had inadequate information to justify a more prominent location for hepatic failure and labeling. One case reported the unlabeled event of respiratory failure in a two week old male who experience seizures, but this case lacked sufficient details for assessment.

Pediatric focused safety reviews for Topamax were previously presented to the PAC in 2011 and again in 2013. Discussions at these meetings largely centered on exploring how to assess the effect of topiramate related metabolic acidosis on the development of potentially serious

adverse outcomes such as decreased bone density, growth retardation and kidney stones.

In order to address some of these safety concerns, FDA issued a post-marketing requirement under PREA in 2011 for a controlled long-term study assessing the effect of topiramate on these potentially serious adverse outcomes in pediatric patients. The final study report is due in September 2018.

This concludes the pediatric focused-safety review for Topamax. We identified no new pediatric safety signals. FDA plans to monitor for anorexia nervosa, bulimia nervosa, and acute hepatic failure in all patient populations. FDA recommends continuing ongoing surveillance. FDA will review the PREA PMR study report once the study is completed.

Does the committee concur?

DR. HUDAK: Thank you, Dr. Khurana. So we are now open for discussion and comment on this. Dr. Dracker?

DR. DRACKER: I think I had something to

do with this original FDA approval going back a couple years for migraines in adolescents. I just wanted to comment. I have never had an adverse reaction in children because I always, for any of the drugs I use, whether it's this drug or any other psychotropic-like drug I always do minimal effective dosing.

So I've seen other colleagues, whether psychiatrists or family practitioners use very high dosing very quickly, and I always found when I use this drug with caution because the side name for it is Topamax not -- which is the biggest complaint patients have when they take this drug. I've never seen that. It's been very safe and it's been very invaluable for children.

DR. HUDAK: Other comments?

DR. TURER: Christy Turer. I had a concerns regarding the anorexia and bulimia, and in reading the cases I do wonder, particularly with the bulimia, if that was a pre-existing condition not brought out by the Topamax which cannot be sorted out.

But in terms of labeling, I do think, you know, there are two approaches. One would be to monitor for anorexia and bulimia over the upcoming year and reconsider this in a year. Another way to go about it would be to say that, in particularly girls with -- any patient, truly, with eating disorders, that clinicians may consider an alternative drug to treat, in particular, migraines.

Just because we use these drugs for weight loss. Topiramate in combination with phentermine (Qsymia). We know in the kids, when I'm treating children with overweight and obesity who have migraines this is particularly effective for them to lose weight. So I think that there's a real risk in prescribing a drug that's known to cause weight loss to patients that have eating disorders.

I think that's important for clinicians to know and to screen for. So I'd be interested in others' thoughts about that. In particular, because, you know, the risk of suicidality or the

risk of death in anorexia is pretty high. And though unrelated in that 16 year old who overdosed, he died. So that's concerning to me. It raised my concern.

DR. HUDAK: Dr. Dracker?

DR. DRACKER: I just want to comment. Some of the information that has come from the adult literature is that the weight loss you see with Topamax can be persistent, even after you stop the drug, and it's not necessarily related to behaviors, whether it's anorexia or bulimia. It's something intrinsic in the drug that really engenders weight loss, and they have continued weight loss after they stop the drug.

My own personal experience, although small, is that I have not seen anorexia or bulimia. I have not even seen weight loss. Only because, I personally, try to go very low dosage to get the effect needed.

DR. HUDAK: Yes. Dr. Anne.

DR. ANNE: It seems like the incidences of anorexia and bulimia is so minimal. It's much

less than the presence in the general population. So, I mean, is there any particular reason to pay attention to these particular disorders? You know, for anorexia it's about slightly less than 1 percent and 1.5 percent in bulimia.

The incidence of this in these particular studies in 0 to 17 group is very small, one to two out of 200 some thousand kids.

DR. TURER: I think my concern is more a risk for abuse. Much like for, you know, a narcotic drug. We'd say in a patient who has known predisposition to drug seeking or, you know, opioid pain drug abuse. You want to really exercise caution in using that drug. I think that the same applies here.

DR. HUDAK: Is someone from FDA able to clarify what there might be in the label about this issue?

DR. HERSHKOWITZ: Hi. Norm Hershkowitz. I'm the epilepsy team leader, but I handle Topamax. Before we put something in the label, first of all, we need good confirmation that this

is an in fact causally related. As kind of suggested by others, as well as our reviewers, there's really insufficient information to determine any causality.

You're suggesting that because there's a potential for abuse based upon its known appetite suppressant effect that we should provide it in the label. I can't think of any precedent where we've done that. This might be listed under a clinical practice. I mean, I can raise it at one of our meetings whether there is -- but you see, we don't think it right now -- we don't have evidence that this is causally. But this is more of a clinical practice decision.

I think some of the others on the panel kind of implied that this might be more of a clinical practice decision. I would like to know, really, what the panel thinks about this. Without a causality, is this a clinical practice decision?

I mean, does one have to be careful, for instance, does appetite suppressants like stimulants have that warning in their label? I

don't know. I don't treat the -- or I didn't treat. I'm now a regulator, of course, for many, many years. But my suspicion is -- maybe what the plan should be to determine if there's a precedent for it, and to look in some of the other appetite suppressants and determine if there is a warning.

Because this is kind of, again, a clinical opinion. I don't know if this satisfied your or if it satisfies the committee. I would be interested to know what you all think.

DR. TURER: Well, that's why I said one of the avenues may be to continue to monitor for this, not add it to the label. But then look over the next year, and particularly as they're a direct drug to population marketing of these things. There are well-connected, you know, blogs and social media things where girls with eating disorder reach out to one another and teach each other about mechanism to help them with appetite suppression.

So, I agree, these are very limited cases, and maybe it bears watching this. I --

DR. HERSHKOWITZ: I believe, isn't that our plan?

DR. TURER: And coming back to it. But I want to stress that this is a concern that I have, particularly given the cases that were presented to us.

DR. HERSHKOWITZ: Well, maybe what I can say is we'll raise this at one of our safety meetings and we'll determine if there is precedent for warning clinicians that there is a potential abuse for this. Although, again, it's -- and we'll see if there's precedent, and maybe I can say that.

But does anybody else from the FDA or -- have an opinion on this?

DR. ALEXANDER: This is Dr. Alexander from the Division of Pediatric and Maternal Health. So I would say that there is clear labeling. I mean, the issue of anorexia and weight loss were identified within the clinical trials. So there is labeling that sort of indicates that this is a known adverse reaction of

the drug. That you have this kind of effect.

So with regards to the issue of labeling for anorexia, I do think that the question does become, you know, how much would we need to do that for other similar drugs that also have that kind of weight loss effect. And so I take the point with regards to the potential concerns about the use of this drug in that population. But then this is a drug that's also -- needs to be prescribed for patients.

So hopefully that type of control is something that people would recognize, especially if it's known that this drug has this issue. That patients with eating disorders will be patients that you might want to avoid such medications in.

DR. HUDAK: Dr. Dracker?

DR. DRACKER: I just want to mention, personally, I think this drug has very limited potential for abuse. Because when you try to take more of this drug for an appetite suppressant purpose the supression is so profound the individuals will not take this for appetite suppression. The

girls really don't like, or boys, don't like taking the medication at high doses because of that effect.

So I think if there was a cultural approach to taking more of this drug to get appetite suppression I think there's better alternatives that wouldn't give them degree of super they're going to experience.

DR. HERSHKOWITZ: Can I say again, my impression listening to the panel and people who have dealt with this drug that this is more of a decision, a personal clinical judgement decision. Although, I think it's worthwhile to continue to examine the issue. But that's my impression that I get from -- you know, I would say a majority, and a small majority because not many people have spoken out on this.

But of those who spoke out on this it -- but, I mean, certainly, we will take this seriously and we'll continue monitoring. I don't personally think a drug safety communication, this is my opinion and may differ, is all that helpful

because I don't think we have enough evidence. Unless we look at other -- you know, maybe this is a global issue if you look at other suppressants.

But, you know, the problem with other suppressants, and this goes for what was previously said, other suppressants certainly have psychogenic propensity to be abused. They give you a high. This gives you more of a low than anything else and confounds you.

So I think it's probably, in sum, it's probably best to just continue monitoring and determine if we establish a signal that's real. This is my feel.

DR. HAUSMAN: Hi. This is Ethan Hausman from Pediatric Maternal Health. Usually the comment I'm about to make comes towards the end of the discussion, but it seems to be relevant now, and I'm speaking a little bit for the pharmacovigilance people.

Routine monitoring includes a robust, ongoing monitoring of FAERS which is the adverse event reporting system. So the fact that the

signals come up, it already means that the signal or potential signal is in the safety evaluator's radar screen. So routine monitoring would not consign this to the dust heap. It means that they would look at it as they usually do when they look through their assignment portfolios.

DR. KAPCALA: Len Kapcala. I'm a medical officer in the neurology division. I just also want to just comment that there's only one approved dose for migraine prophylaxis in adults and adolescents. So, I mean, if you're using lower dosing or higher dosing it's not approved or recommended dosing.

DR. HUDAK: It's within the realm of individual subscriber discretion for the lower dose.

DR. LEVIN: Hi. This is Bob Levin from FDA pharmacovigilance. Dr. Turer, you raise a lot of excellent points, obviously. We do plan on -- it's high on our list for this drug of continuing to do specific monitoring for these possibilities of abuse, misuse, and just eating

disorders in general. Dr. Long here will be doing that, specifically.

Also, the other good points you raise are about how, like in many populations, eating disorder populations may be quite sophisticated and clever about what they might do, surreptitiously or otherwise. I think you made a point about possibly monitoring, in addition to regular routine pharmacovigilance of our FDA adverse event database it is something worth looking into other venues on the web to see if -- that often does produce a lot of useful information. So I think it's another great suggestion that we'll look into.

DR. HUDAK: I think we had a question. Dr. Cunningham?

DR. CUNNINGHAM: Melody Cunningham. I had a question. I did look through the FDA label for methylphenidate and there is nothing about eating disorders in that label.

DR. HUDAK: Okay. Any other comments. So, in summary, it appears that there is

reasonable information in the label for Topamax that practitioners can put two and two together here on a risk assessment, and that the FAERS and other monitoring has identified this as a new issue, and that you're intent on looking at this with increased fervor going forward.

So I would call the question to vote then about the recommendation to continue the ongoing surveillance with specific attention to these issues of eating disorders and acute hepatic failure. So a yes vote, no vote, abstain on your speaker.

DR. LONG: This is Karen Long, safety evaluator from Division of Pharmacovigilance. I just wanted to mention. This is on the radar for us for monitoring, and because of the reasons that you discussed. I can tell you that from our weekly monitoring of the reports that there are no other reports of this.

So this is why it came up on the radar because when we were doing this review, we do realize that these are important adverse events,

especially in adolescent aged individuals. But we have not seen any other reports besides the ones that are reported here. That gives you a little.

DR. HUDAK: Okay. Is voting concluded? Everybody has voted? So can we see that? Okay. We'll go around the room. Dr. Fischer first.

DR. FISCHER: Gwen Fisher. I agree.

DR. MOON: Mark Moon. I agree.

DR. SAVEL: Wael Savel. I concur.

DR. HAVENS: Peter Havens. Yes.

DR. TURER: Christy Turer. I concur. And I'd just like to state that the difference between methylphenidate and topiramate is that methylphenidate is not part of an FDA approved drug for weight loss. That's the key point.

DR. SHWAYDER: Shwayder. Concur.

DR. CNAAN: Avital Cnann. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. CUNNINGHAM: Melody Cunningham. Concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. DRACKER: Bob Dracker. I concur. I would just want to comment that we should monitor unexplained weight loss, not necessarily just anorexia or bulimia.

DR. WHITE: Michael White. Agree.

DR. WADE: Kelly Wade. Agree.

DR. ANNE: Premchand Anne. Concur.

DR. HUDAK: Okay. So the summary there is that the committee unanimously agrees with the FDA recommendation to continue monitoring with attention to these several issues.

(Recess)

DR. HUDAK: We'll get started now. FDA people at the table can introduce yourselves, we'll get started here.

DR. HARINSTEIN

: Lisa Harinstein.

Division of Pharmacovigilance.

DR. DANNIS: Marjorie Dannis, Division of Gastroenterology and Inborn Errors Products.

DR.RAJPAL: Anil Rajpal, clinical team leader, Division of Gastroenterology and Inborn Errors Products.

DR. GREENE: Patty Greene, Division of Epidemiology.

DR. HUDAK: Very good. So we have Dr. Radden, you're here for a doubleheader. Okay. So you will present first on these three products. Asacol and Asacol HD and Delzicol. Maybe in the course of your presentation you can clarify for us whether we should be voting on your recommendations separately or as a unit, perhaps.

DR. RADDEN: All right. Good morning. So, as mentioned, I'll be discussing the pediatric focused safety review for these three mesalamine products, Asacol, Asacol HD, and Delzicol. I'll be following the outline shown here.

So there are currently eight FDA approved mesalamine products marketed in the U.S., all of which are noted here with various formulations, routes of administration, approved indications, and approved populations for use. While this review focuses on Asacol, Asacol HD, and Delzicol, data for all mesalamine products were also evaluated. Asacol and Delzicol,

however, are the only mesalamine products approved for use in children.

So mesalamine is an aminosalicylate indicated for the treatment and maintenance of remission of mildly to moderately active ulcerative colitis or UC. Asacol and Delzicol are approved for both treatment and maintenance. However, only the treatment indication is approved in pediatric patients down to 5 years of age. Asacol HD is only approved for treatment of moderately active UC and only in adults.

Asacol and Asacol HD are delayed release tablets in 400 milligram and 800 milligram doses, respectively. Delzicol is a delayed release capsule that contains four smaller 100 milligram tablets. Pediatric dosing for Asacol and Delzicol is weight-based with a maximum of 2.4 grams daily, divided in two doses.

Asacol was approved in 1992 followed by Asacol HD in 2008, and most recently Delzicol was approved in 2013. There have been multiple pediatric labeling changes for these three

products. Though, initial pediatric labeling for these products occurred in October 2013 for Asacol and Asacol HD. In April 2014 for Delzicol which triggered this safety review.

Based on these labeling changes, Asacol and Delzicol are currently approved for the treatment of UC in patients 5 years and older, but none of the products are approved for maintenance of UC in pediatric patients. However, there is a pediatric study requirement pending to evaluate Delzicol for maintenance.

I want to pause at this point to highlight a few safety activities that have occurred in order to provide additional context to the background information for these products. FDA became aware of a potential reproductive and fetal developmental effects with dibutyl phthalate, an excipient in Asacol and Asacol HD. In March 2009, asked the sponsor to develop formulations without this excipient.

The sponsor complied and Delzicol was developed as a phthalate free formulation to

replace Asacol. Following Delzicol's approval in February 2013, Asacol was removed from the U.S. market in March 2013. Additionally, a new phthalate free formulation of Asacol HD was approved a few months ago in May 2016.

Furthermore, in April 2014, the Division of Pharmacovigilance evaluated 53 post-marketing reports of Delzicol related to difficulty swallowing and drug administration errors. They provided recommendations to update Delzicol labeling and request further monitoring by the sponsor. However, following a review by the Division of Gastroenterology and Inborn Errors Products, in July 2015, the noted safety concerns were subsequently mitigated by the approval of the currently marketed formulation of Delzicol, containing the four smaller tables within one capsule.

Now I'll continue with the pediatric study supporting the labeling changes for this safety review. Efficacy for Asacol and Delzicol in pediatric patients was supported by adequate

and well-controlled studies of Asacol in adults in addition to a single study of Asacol in 82 pediatric patients 5 to 17 years of age, and a demonstration of bioequivalence between Asacol and Delzicol.

However, one Asacol HD tablet was not demonstrated to be bioequivalent to two Asacol tablets. Therefore, dosing could not be established for Asacol HD to support pediatric approval.

A pediatric study was conducted for maintenance of remission of UC with Asacol. However safety and effectiveness was not established. Likely related to premature termination of the trial and the dose range studies.

Ultimately, the labeling changes associated with Asacol include changes to Section 8.4 which describes how safety and effectiveness have been demonstrated in patients

years and older for treatment, but not in patients less than 5 years of age nor for the

maintenance indication in any pediatric age group.

Additionally, pediatric PK, dosing, adverse reactions, and clinical trial data were included throughout labeling. Similar changes were made to Delzicol labeling. Labeling for Asacol HD directs prescribers to other approved mesalamine products for information on pediatric use.

Now, before we look at the use of Asacol, Asacol HD, and Delzicol I want to note some of the safety labeling for these products which will be discussed again later in the review. Note that both the warnings and precaution section, and the post-marketing experience subsection include information on interstitial nephritis.

Now let's look at use. This table displays the nationally estimated number of patients with a dispensed prescription for Asacol HD and Asacol from U.S. outpatient retail pharmacies during the review period of October 2014 through February 2016. You'll notice that

pediatric patients 0 to 17 years accounted for approximately 3 percent of total patients with a dispensed prescription for both Asacol HD and Delzicol. Patients 5 to 17 years of age accounted for the vast majority of pediatric use. A similar trend is noted with Delzicol.

Now, let's turn our attention to the safety and pediatric focused adverse events. The review included a search for all mesalamine products from the approval day of the first marketed mesalamine product in December 1987 to February 2016. You'll notice that of the 535 events reported for pediatric patients, 385 were deemed serious with 19 deaths.

Now I'll walk you through the selection of the final case series. Of the 385 serious pediatric reports, 381 were reviewed and excluded from the pediatric case series for the various reasons listed here. Note that of the 19 reports with an outcome of death, seven reports were duplicates, six reports describe transplacental exposures, and one report had insufficient

information to assess causality. The remaining five reports involved patients receiving multiple immunosuppressant medications who died as a result of strong alternative causes, including hepatosplenic T-cell lymphoma, hemophagocytic syndrome, disseminate intravascular coagulation secondary to bacteremia, and Epstein-Barr virus associated lymphoproliferative disorder.

That left us with four cases and no deaths. Of the four unlabeled, non-fatal, serious adverse events, two involved benign intracranial hypertension, and two involved nephrogenic diabetes insipidus.

The first case of benign intracranial hypertension or BIH involved a 15 year old female who developed neck pain, headache, and scotoma one month after starting Pentasa, another mesalamine product. She was diagnosed with BIH and papilledema, and most of her symptoms resolved with reduction of the mesalamine dose, and addition of acetazolamide.

Following a UC relapse three months

later, mesalamine was discontinued and corticosteroids were initiated, but her scotoma persisted.

The second case involved an 11 year old female who developed worsening headaches after starting an unspecified mesalamine product. She was found to have optic disc edema and elevated erythrocyte sedimentation rate, and a normal head CT. Following discontinuation of mesalamine and initiation of corticoid steroids her symptoms partially resolved.

Based on these findings, the Division of Neurology Products reviewed these two cases, in addition to another case report of BIH in a 23 year old female. However, the division was unable to distinguish whether the cases were the result of BIH or cerebral venous thrombosis. Due to insufficient imagine, responses to acetazolamide or corticosteroids, and the association of both of these conditions in patients with inflammatory bowel disease.

Two cases associated with nephrogenic

diabetes insipidus or NDI and interstitial nephritis were also identified. Recall that mesalamine products are currently labeled for interstitial nephritis.

The first involved a 14 year old female who developed NDI and interstitial nephritis approximately five months after starting another oral mesalamine product for the treatment of UC which was confirmed with water depravation and vasopressin testing and renal biopsy. Following discontinuation of mesalamine and initiation of a corticosteroid, the NDI resolved and the interstitial nephritis partially improved. However, drug induced lymphocyte stimulation testing was positive for mesalamine.

In the second case, a 9 year old male being treated for UC developed interstitial nephritis without confirmed histopathology, and NDI after the increase of another oral mesalamine product, and the addition of mesalamine rectal enema. His symptoms resolved after mesalamine was discontinued.

The Division of Cardiovascular Renal Products conducted a review of this safety concern, and it concluded that the events of NDI were likely drug related and recommended that NDI be added to the list of adverse reactions in the post-marketing section of product labeling for those drugs labeled as causing tubule interstitial nephritis.

This concluded the pediatric focused safety review. The review identified benign intracranial hypertension as a safety signal. However, imaging was insufficient to distinguish the event from cerebral venous thrombosis. Nephrogenic diabetes insipidus was also identified as a safety signal. Based on the available data, the FDA recommends no changes to mesalamine product labeling for benign intracranial hypertension at this time.

However, FDA recommends adding nephrogenic diabetes insipidus to the list of adverse reactions listed in the post-marketing section of mesalamine product labeling. FDA also

recommends continuing ongoing routine pharmacovigilance monitoring.

I'd like to acknowledge my colleagues on this slide for their assistance.

DR. HUDAK: Thank you.

DR. RADDEN: So, in response to your question, we looked at the review of mesalamine products as a whole, so I believe that you can consider the questions that we are posing in our recommendations as a whole for all mesalamine products.

DR. HUDAK: Thank you very much. Dr. White?

DR. WHITE: I've been accused of looking at the data too closely, but I have something that's confusing me. Asacol was taken off the market in March of 2013 and the table that we have in our data that we were given for review, October 2013 to February 2016 there 3,700 prescriptions, apparently, that were given out after the drug was removed from the market.

In that same diagram or that same chart

is labeled as 2014 to 2016 in your presentation. Is that just a problem with the way we're compiling the data, and where it's coming from, and the way it's presented to us in the different databases? That you could have 3,700 prescriptions dispensed after it was taken from the market?

DR. RADDEN: I'll have to defer that to the use.

DR. GREENE: This is Patty Greene. Yes, we actually have residual prescriptions that actually trickle down in our data for longer than after the product is taken off the market. So it's very common to see that. We have trickling of prescriptions that are still in the system.

DR. WHITE: How do I know which dates to believe because the numbers are identical? Is it from October 2014 or October 2013?

DR. GREEN: Oh, I'm sorry.

DR. WHITE: It's the same numbers in two different places. One is in the data we were given for review and then the other is in the

chart and the slide.

DR. GREENE: I'm sorry. That's an error. It should be October 2013.

DR. WHITE: Okay.

DR. GREENE: Yes.

DR. WHITE: Thank you.

DR. HUDAK: Okay. So this is open for discussion. Interesting, two different conclusions about safety signals. Any comments? Dr. White, you were saying something?

DR. WHITE: Not intentionally.

DR. HUDAK: Okay. Yes, we have a question over here. Yes?

DR. SAVEL: So are we voting separately on whether to include benign intracranial hypertension as another adverse event -- adverse effect or --

DR. HUDAK: Well, the vote would be on the recommendation as it stands which is both things, so that's why I was trying to elicit comment as to whether or not one wanted to separate those out.

DR. SAVEL: Because this is -- I'm Wael Savel from pediatric GI, University of Connecticut. Couple of things. The Delzicol switch came about in 2014 and I remember precisely where I had to change my patients from Asacol to Delzicol because Asacol was no longer available. So there was a sudden switch that we had to deal with.

Number two, one of the frequency side effects that we see with these patients is headaches. I quite honestly believe that the benign intracranial hypertension is underdiagnosed in many of these patients because the usual thing that we do is discontinue the medication without any further testing. We just report it has headaches instead of benign intracranial hypertension which is probably contributing to a significant portion of those patients who did develop headaches.

Thirdly, the medications are approved for pediatric patients ages 5 and above. However, I quite honestly can't remember the last time I've

seen a 5, 6, 7 year old prescribed Delzicol or Asacol. Due to the fact that the tablets are very large or the capsules and they are unable to swallow them, and it is not recommended to open up those capsules either.

So therefore, we end up using off-label medications we recommend for the patients to open and mix with applesauce or whatever their preference is and consume those medications. The interstitial nephritis is a very well-known adverse event that we see with these patients. Diabetes insipidus, however, I've seen one case in ten years of practice and it's not a very common phenomenon.

As mentioned with those cases, once you discontinue the medication the symptoms reverse, at least from the case I've seen also. Thank you.

DR. HUDAK: Perhaps we could just prepare to put up the section on the adverse event labeling for these products. Does that include headaches or...

DR. HAUSMAN: I have the label. Hold

on. Ethan Hausman, DMPH. Headache is listed under pediatrics in adverse reactions. Section 6.1, so that's actually in relation to control data.

DR. HUDAK: Dr. Campbell?

DR. CAMPBELL: Do you know what imagine the 23 year old had with pseudotumor? Did she have an MRI or other imaging?

DR. RADDEN: I'll defer to the safety.

DR.HARINSTEIN: Hi. I can respond to that. So the 23 year old had a CT, MRI, and an LP performed, but there was no additionally venous imaging on the MRI.

DR. CAMPBELL: So, in general, a regular MRI is sufficient to look for venous thrombosis, so how did you all reach the conclusion that you couldn't rule that out based on the imaging?

DR. HARINSTEIN: We had consulted the Division of Neurology Products and the medical officer there had recommended that because of the imaging and the other two pediatric cases that it was insufficient for a diagnosis of BIH versus

cerebral venous thrombosis.

DR. HUDAK: Dr. Hoehn?

DR. HOEHN: Sarah Hoehn. So I had a follow up to what Dr. Campbell was saying. Cerebral venous thrombosis, by definition, is not benign and it's not going to resolve by itself. So it wouldn't -- the fact that the treatments resolved without treatment or intervention or anticoagulation, to me, means it's unlikely that it was venous thrombosis.

So it seems like the rationale given for not adding it to the labeling change doesn't really hold up. I would advocate adding benign intracranial hypertension to the labeling change the same and interstitial nephritis. I think that's a really, in my opinion, a very weak argument given to not add it just because they didn't do an angiogram to a clot. The fact that their symptoms got better. That's my thoughts. But I certainly defer to Dr. Campbell.

DR. HUDAK: Dr. Campbell?

DR. CAMPBELL: Did you consult with a

radiologist or just a neurologist? Because I haven't met a neuroradiologist who could not diagnose a venous thrombosis based on a plain MRI without an MRI venogram.

DR. HARINSTEIN: Just a neurologist. However, the neurologist felt also on the case of the 23 year old that the open pressure (inaudible) was higher than he has typically seen, some concern in the case.

DR. CAMPBELL: Could you clarify that comment? By definition, when you have pseudotumor you have an elevated open pressure with an LP.

DR. HARINSTEIN: The opening pressure is 80 centimeters of water in the case, and he felt that that was higher than he's typically seen in these patients.

DR. CAMPBELL: I don't understand how that differentiates between a cerebral thrombosis versus a drug induced pseudotumor.

DR. HARINSTEIN: It wouldn't have helped to distinguish that. He was just unsure about the credibility of the case.

DR. HUDAK: So I guess the question here is do we have two or three cases of benign intracranial hypertension?

DR. HARINSTEIN: We have three cases. Two in pediatric patients, specifically. The 23 year old was not the pediatric patient, obviously.

DR. HOEHN: This is Sarah Hoehn. But we have the same number of pediatric patients with interstitial nephritis which we're saying we should add a labeling change. We have the exact same number of patients who fulfill diagnostic criteria for intracranial hypertension, and we're willing to not add that. That's what is troubling to me.

DR. FISCHER: This is Gwen Fischer. I would agree with that statement and also add that none of the patients in these cases had other signs of venous thrombosis. Typically you would see signs of stroke and seizure which is fairly common with those patients.

DR. HUDAK: Okay. So I think we will separate this into two votes. The first vote

would be for the whole category of all the mesalamine products available for pediatric treatment. Whether to agree with the FDA recommendation not to change the labeling regarding benign intracranial hypertension with this product. So we'll do that vote first.

So you can indicate -- so, in other words, if you say yes you agree that there shouldn't be any product labeling change. If you say no you would suggest that there is a change and then we'll sort of take the vote and see where we are, so.

There we go, okay. So let me make sure that I understand the data. So the data are, the red is the no vote?

UNIDENTIFIED MALE: Yes.

DR. HUDAK: Okay. And the green is the yes. Okay, so we'll go around the table and folks can provide their rationale. We'll start over here with Dr. Anne.

DR. ANNE: Dr. Anne. No.

DR. WADE: Kelly Wade. No.

DR. WHITE: Michael White. No. I think that the instance of headache is quite high or at least recognized as a problem and may very well be related to intracranial hypertension that never gets worked up.

DR. DRACKER: Bob Dracker. No.

DR. HOEHN: Sarah Hoehn. I voted no. I think benign intracranial hypertension should be added to the labeling change.

DR. CUNNINGHAM: Melody Cunningham. I voted yes, but I was thinking not clearly and, no, I think it does need to be added to the label.

DR. CAMPBELL: This is Jeff Campbell. I voted no. I think when you have a kid with pseudotumor we often start looking through the list of drugs that cause pseudotumor, and I think these two cases sound pretty compelling and it would be valuable to have this on the list.

DR. CATALETTO: Mary Cataletto. I voted no.

DR. CNAAN: Avital Cnaan. I abstained because I felt that I didn't have enough

information. Hearing some additional information as people went around, I will join the no.

DR. SHWAYDER: Shwayder. I voted yes under the assumption that headache would lead people to look for these other things, and it's already listed as headache as a side effect.

DR. TURER: Christy Turer. I voted no. I think -- I agree that we look for what drugs cause intracranial hypertension. I think it would be valuable to add this.

DR. HAVENS: Peter Havens. I voted no. I agree.

DR. SAVEL: Wael Savel. I voted no. I completely agree with the statements by Dr. White, and I think it's an underdiagnosed side effect.

DR. MOON: Mark Moon. No.

DR. FISCHER: Gwen Fischer. No.

DR. HUDAK: Okay. I think that's a pretty clear signal. We'll vote on the second part of the recommendation, and that is whether or not you agree, yes, or disagree, no, with the FDA recommendation to add nephrogenic DI in the

post-marketing section on adverse reactions. So please vote.

Again, a pretty clear signal. Dr. Fischer, we'll start with you.

DR. FISCHER: Gwen Fisher. I concur.

DR. MOON: Mark Moon. I concur.

DR. SAVEL: Wael Savel. I concur.

DR. HAVENS: Peter Havens. Yes.

DR. TURER: Christy Turer. I concur.

DR. SHWAYDER: Shwayder. Yes.

DR. CNAAN: Avital Cnann. Yes.

DR. CATALETTO: Mary Cataletto. Yes.

DR. CAMPBELL: Jeff Campbell. Yes.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. Yes.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. I agree.

DR. WADE: Kelly Wade. I agree.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: So, in summary, with these two votes the committee agrees with adding

nephrogenic diabetes insipidus, but disagreed with not adding benign intracranial hypertension. Just a point of semantics that's been raised, is that sufficient to be construed as a recommendation to add it or do we need to take a separate vote on benign intracranial hypertension?

DR. ALEXANDER: This is Dr. Alexander. I think we got the message.

DR. HUDAK: Pardon me?

DR. ALEXANDER: I think we got the message.

DR. HUDAK: Okay.

DR. NELSON: If not A doesn't mean if not B.

DR. HUDAK: There was a question, so I was just making sure. Thank you.

DR. LEVIN: Excuse me, Dr. Hudak? May I?

DR. HUDAK: Yes.

DR. LEVIN: A couple more points. Again, Bob Levin, pharmacovigilance. We will, as soon as possible, take that under discussion with

neurology colleagues and look in more detail. The other thing we can do, we'll go back and look at our searches and maybe broaden our search to see if we can capture such cases in a different way.

May I also ask Dr. Savel a question? You mentioned that intracranial hypertension is under recognized, underdiagnosed. Did you mean broadly is that a general comment?

DR. SAVEL: I think broadly in patients who are treated with mesalamine preparations. As I mentioned earlier, they are diagnosed with headaches which is one of the common side effects, with or without other symptoms. Usually the symptoms occur two weeks to four weeks after initiation of the medication regardless whether the patients are on steroids or not, on concomitant steroid treatment or not.

Therefore, the general practice is to stop the medication and see if the symptoms resolve or not. Frequently, the symptoms do resolve or more frequently than not. And therefore, without any further testing we have

made the diagnosis that the patient has an adverse reaction to mesalamine and we stop the medication and we moved on to a different medication without looking at benign intracranial hypertension.

I certainly have seen at least two or three cases in the last five years that, for sure, fit the criteria.

DR. LEVIN: Right, okay. That's really helpful. Appreciate it.

DR. SAVEL: Yes.

DR. HUDAK: Okay. Great. So we will move on, I think, to a discussion of Kepivance. Dr. Radden, you have the floor again.

DR. RADDEN: I'll wait for the --

DR. HUDAK: Oh, we have a new FDA group coming.

DR. RADDEN: Yes.

DR. HUDAK: Okay. If those arriving at the table could introduce yourselves to us.

DR. PATAVANICH: Saharat Patanavanich, safety evaluator with Division of Pharmacovigilance.

DR. DINNDORF: Patricia Dinndorf, clinical reviewer from the Division of Hematology Products.

DR. MISTRY: Kusum Mistry, drug use analyst, Division of Epidemiology.

DR. RADDEN: All right. I'll get started. So today I will also be discussing the pediatric focused safety review for Kepivance or palifermin. I'll be following the outline shown here.

Kepivance is a mucocutaneous epithelial human growth factor. It is indicated to decrease the incidence and duration of severe oral mucositous in patients with hematologic malignancies receiving myelotoxic therapy in the setting of autologous hematopoietic stem cell support.

Dosing recommendations advise intravenous injection of 60 micrograms per kilogram per day for three consecutive days before and three consecutive days after myelotoxic therapy, for a total of six doses.

Kepivance was originally approved in

December 2004. In May 2013 data from a pharmacokinetic and safety study supporting use in patients 1 to 16 years of age was adding to labeling which prompted this safety review. Additionally, there is a pending pediatric post-marketing study that is due in March 2020 to evaluate survival, incidence of secondary malignancies, cancer relapse, hospitalization days, and treatment related complications in hematopoietic stem cell transplant recipients.

Use of Kepivance in patients 1 to 16 years of age is supported by adequate and well-controlled studies in adult, in additional to a dose escalation, PK, and safety study of 27 pediatric patients with acute leukemia who underwent myeloablative therapy and hematopoietic stem cell transplant.

Subsection 8.4 of Kepivance labeling was updated to describe the limited supporting use -- data supporting use in patients 1 to 16 years of age, including the results of this PK and safety study.

I would also like to call your attention to additional label changes relevant to safety which were recently completed following an evaluation of the risk of infection in studies of Kepivance in the transplant population. While no increase incidents of infection was noted in the two studies that supported approval, an increased incidence of treatment emergent infections was noted in a post-approval study of patients with multiple myeloma who underwent autologous transplantation with a chemotherapy only preparative regime using high dose melphalan.

In this study, shorter timing between pre- and post-preparative Kepivance regimens compared to the two studies that supported approval was noted. Additionally, findings form a study of Kepivance with allergenic transplantation were evaluated. No increased risk of infection was identified. However, the study also did not demonstrate efficacy in decreasing the incidence of severe, acute graph versus host disease. And there was a higher incidence of severe mucositis

in Kepivance patients.

Based on the analyses of these studies, labeling was changed to revised the dosing schedule to ensure seven days between pre- and post-preparative regime doses. And to add information on the increased risk of infection in the melphalan study.

Additionally, in the setting of allergenic transplantation, a limitation of use statement and a discussion of the increased incidence of severe mucositis was included.

Now let's look at the use of Kepivance. This table displays the nationally estimated number of patients with a hospital discharge billing for Kepivance from U.S. non-federal hospitals from the date of the pediatric labeling change in May 2013 through December 2015. Of the nearly 1,400 total patients, pediatric patients account age

to 16 years old accounted for approximately 17 percent of the total Kepivance use. No use in patients less than 1 year of age

was captured.

Now I'll review the safety and pediatric focused adverse events associated with Kepivance since the start of FAERS data collection in January 1969 through March 2016. As you can see, of the eight events reported for pediatric patients seven were classified as serious with one death.

Now let's walk through the selection of the pediatric case series. Of the seven serious pediatric reports four were found to be duplicates and excluded, leaving three deaths -- I'm sorry, three cases and one death. Of the three serious pediatric adverse events there was one fatality, one case involved the unlabeled events of cardiac and hepatic failure, and one case involving the unlabeled event of seizure.

The one fatal event involved a six month old female with complicated cardiopulmonary history, including severe and progressive respiratory issues that was ultimately treated with Kepivance off-label based on a potential

pulmonary benefit. She died three weeks later due to respiratory insufficiency and pulmonary hypertension which resulted in right ventricular failure. Her demise was associated with her multiple underlying medical issues and unlikely related to Kepivance use.

The first nonfatal serious adverse event involved a 13 year old male with clear cell renal sarcoma treated with doxorubicin. He was subsequently given Kepivance for mucosal inflammation and developed cardiac and hepatic failure 10 months after starting Kepivance and eight months after his last dose.

The case is confounded by the use of doxorubicin which is associated with cardio toxicity. Additionally, insufficient information was provided to assess causality for the hepatic failure.

The last case involved a 4 months old female with a reported past medical history significant for Omenn Syndrome, a form of severe, combined immunodeficiency who was taking multiple

medications. She developed a rash and seizures two days after starting Kepivance, and three days after starting cyclophosphamide prior to a stem cell transplant. Note that skin rash is a labeled event and the event of seizure is confounded by the concomitant use of multiple medications.

FDA also review reports of a clinical and a non- clinical study evaluating Kepivance to improve pulmonary outcomes. Both post-marketing studies were associated with worsened outcomes, including increased risk of mortality and infection with Kepivance use in these settings. Additionally, use of Kepivance in these studies involved dosing and/or a route of administration different from approved recommendations.

This concludes the pediatric focused safety review. Overall, the cases were either related to the patients' underlying medical conditions, confounded by concomitant medications, or had limited information to assess causality. No new safety signals were identified. However, the review highlighted risks associated with off-

label use of Kepivance for pulmonary indications which should be discouraged unless a benefit in this setting is demonstrated.

FDA recommends continuing ongoing surveillance. Does the committee concur? Again, I'd like to acknowledge my colleges on this slide for their assistance.

DR. HUDAK: Thank you, Dr. Radden. I'd just comment that I think the one death you saw was a incredibly last ditch effort to try something that might be beneficial to a child who was on death's door and was unsuccessful.

When was this case? Do you know? Just out of curiosity.

DR. RADDEN: You said when was it?

DR. HUDAK: Yes, when was it?

DR. RADDEN: I'm not sure.

DR. HUDAK: Was it still in the era when we were using a lot of chloral hydrate?

DR. PATAVANICH: The case was reported back in 2012.

DR. HUDAK: 2012, okay. Hepatoblastoma

is something that's been linked to chloral hydrate use in this children.

Okay. This is open for discussion.

DR. SHWAYDER: Using this medicine, the mucous in the mouth is different from the mucous in the lungs. Were they just stabbing at something? Why were they using it?

DR. HUDAK: I have no idea, but presumably that's what it was.

DR. DINNDORF: There was some -- as far as the study in adults, they were basing it on some pathophysiology where they thought that it might be useful in quickening recovery of patients who had acute respiratory syndromes, and it was given IV. In a schedule that's not at all like the schedule -- it was continuous over a number of days.

In the animal study, the dog was given intranasal into rats who were given doses of virus concomitant. The dose that was delivered was several orders of magnitude more than the dose that would be given at the indication. Then there

was in the rats who had received the Kepivance in addition to being -- receiving the virus there was an increase mortality. It was mice, not rats. I always get that mixed up.

DR. HUDAK: So the question is open for a vote and that is the FDA recommends no label changes and continue their ongoing surveillance process. So vote on your machine.

Okay. So we'll just go around the room to formalize it. So we can start with Dr. Fischer.

DR. FISCHER: Gwen Fisher. I concur.

DR. MOON: Mark Moon. I concur.

DR. SAVEL: Wael Savel. I concur.

DR. HAVENS: Peter Havens. Concur.

DR. TURER: Christy Turrer. I concur.

DR. SHWAYDER: Shwayder. Concur.

DR. CNAAN: Avital Cnann. Concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CUNNINGHAM: Melody Cunningham. I

concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. I agree. Although, I'm not sure how you're going to discourage off label use without making a change in the label.

DR. WADE: Kelly Wade. I concur.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: Okay. So in summary, unanimous agreement with the FDA recommendation on Kepivance.

DR. DINNDORF: Can I make a comment about the off-label use? We tried to negotiate that with the sponsor to actually include comments, more detailed information about those two incidences. We got push back from the sponsor, and we do not have regulatory authority to make them do that. we would have preferred to do that.

DR. WHITE: I understand that.

DR. HUDAK: Okay. So that concludes staff product review. Are we still on schedule to

move to the update on EXJADE?

MARIEANN BRILL: Yes.

DR. HUDAK: So this is -- a couple comments on this. This is an issue that was identified from a public hearing about a year ago, as you heard this morning. The FDA has been working on this. This is sort of an interim, not a final, sort of progress report as to the status.

No one on the committee, because this sort of came up as a late addition has been cleared for conflict of interest on this, so this is for information only. So there can be do opining from the committee on any of the matters that are presented.

So I think Dr. Waldron, you're set to go?

DR. WALDRON: Yes, I am.

DR. HUDAK: Anybody else at the table? No, no one else at the table we need to introduce, so thank you.

DR. WALDRON: My name is Peter Waldron. I'm the representative of a group which is

evaluating the safety issue raised at the September 2015 Pediatric Advisory Committee regarding *deferasirox.*

Since one year has elapsed from this request we want to tell the committee and other interested parties how we are addressing this concern. First, I will review the presentation to the September 2015 PAC briefly and give a high level overview of our plan. Then I will discuss the safety issues of fever, dehydration, or hypovolemia and renal and hepatic injury. Finally, I will describe the data sources that we will use.

The case presented at the PAC was part of the scheduled review of deferasirox. A child with a fatal outcome was identified by the review. This child's mother also presented her daughter's case to the PAC, and there were additional comments about the child's case from the Cooley’s Anemia Foundation.

In brief, the child was a 35 month old girl who had transfusion dependent thalassemia.

She developed an acute illness while she was receiving deferasirox. When she presented for medical attention she had kidney and liver failure and metabolic acidosis. A diagnostic test for a respiratory syncytial virus was positive.

Her immediate cause of death was cerebral edema with herniation. The PAC's specific request to the agency, as communicated by this quote in the first bullet was to evaluate the acute illness event, fever. In developing the analysis plan we began the process of reviewing fever as an indicator to interrupt *deferasirox* dosing. However, we concluded early in this process that a broader interpretation of fever to mean an acute illness including fever and hypovolemia was needed.

I will describe this evaluation in more detail with the next slides. Having determined this focus, then we are identifying cases from the sources available to us which I also will describe later. We will then analyze the events of kidney and liver injury with a goal of identifying pre

disposing factors and potentially preventable causes.

We are focusing on liver and kidney injury because these are the organ systems that are most frequently adverse effected by deferasirox. Then, using these sources we will analyze the role of interrupting or continuing deferasirox during acute illness events. With a goal of determine how the decision to continue or interrupt may influence the outcome of acute illness events relative to kidney and liver injury.

As healthcare providers to children, you know that when we observe a large group of children over months and years a high proportion will have at least one illness with fever. The figure of 45 percent of pediatric subjects with fever is from the sponsor's investigator's brochure. This proportion represents the sponsor's current aggregation of clinical trial findings.

Since assessing fever is a part of our

review, we will develop our own result for the proportion of children who develop fever. However, acute illness, including some viral infections, illnesses with hypovolemia and anorexia, and acute liver injury can develop without fever. Therefore, as part of our evaluation we plan to assess acute illness events with and without fever, and their outcomes including the variable of dose interruption.

Hypovolemia, due to decreased intake, and/or increased loses, both insensible and measureable, is a common component of pediatric illnesses. Clinical trials with deferasirox establish that renal injury is a risk of deferasirox use. The deferasirox label includes statements about monitoring renal function and dose reductions and interruptions for compromised renal function.

Since hypovolemia can compromise renal function we considered hypovolemia to be an important component of acute illnesses that we should evaluate. Therefore, we will determine the

potential for acute volume loss to produce labeled renal criteria for dose modification, and the potential for volume loss to produce excess exposure.

Now, we acknowledge that unlike temperature, there is not a straightforward measurement in the absence of a recent baseline weight to assess volume loss. Through our clinical parameters that are used to develop estimates of volume status, including mucous membrane moisture, tear production, skin quality, the appearance of eyes and heart rate, as well as laboratory parameters that can be used in clinical settings to make an assessment of volume status.

However, the FDA reviewers do not have the patient and the hospital lab in front of us. We are limited to the reported data, so our estimates of volume status will be more limited than a clinician at a bedside.

In summary, we identified the events fever and hypovolemia as indicators of acute illness. We will evaluate those events for their

association with kidney and liver injury. The data sources that we have available to examine a relationship between acute illness events and subsequent adverse events are listed here. The five year observational study among children ages 2 to less than 6 at enrollment was submitted to the FDA January 29 of this year for the purpose of fulfilling a post-marketing requirement.

The second source listed here is a pooled analysis of 17 studies that included pediatric AIDS subjects. The sponsor submitted these and other datasets in responses to our request. The FDA Adverse Event Reporting System is another source that we will use to identify cases of fever or hypovolemia, and finally, the medical literature.

In conclusion, we expect to make a final report the Pediatric Advisory Committee in March of next year. At that time, any change to the label that the agency may recommend will be discussed.

DR. HUDAK: Thank you. Very clear

presentation of the issue. If anyone has any questions or they want to illicit more information from Dr. Waldron that's fair. But otherwise we'll wait for your report in March. Thank you.

DR. WALDRON: Thank you.

DR. HUDAK: Moving on, we'll end the morning with a presentation. I assume this is Lieutenant Commander Dr. Dinatale coming up to present on, I think a very interesting summary, on the new pregnancy and lactation labeling rule.

DR. NELSON: So, Mark, as they're getting set up let me just give a quick context. So you may notice at times when we do that little chart that says, here's the things that are included in the review, you know, pre, what do we call it, prenatal, whatever. Exposure during pregnancy it sort of slides over to one side.

Basically, we thought it would be useful to give you a sense of that labeling rule, and I might call your attention when you get to it, as to where the labeling changes when companies have to convert to the new PLLR that there's a complete

review of data at that time. We're also in conversations with DPMH, the Maternal side of the pediatric maternal health about the review of those, you know, pregnancy exposures.

So the feeling is that it's not part of the PAC remid, if you will, in terms of pediatrics. If there was an issue we would bring it back, but we thought it would be useful for you to see exactly what's going on, if you will, on that side of the house relative to those -- I mean, one of them was, like, 85. I mean, you see those cases disappear. We wanted to have some sense of where they're going.

DR. DINATALE: Okay. Good morning. Thank you for that introduction. So this morning we will be discussing the pregnancy and lactation labeling rule, also known as the PLLR. So here's my overview. We'll start with a brief introduction. We'll look at the history of pregnancy labeling. I'll provide you with an overview of the PLLR labeling changes, and then we'll go through a summary and conclusion.

So there are 6 million pregnancies in the United States every year and 50 percent of women report taking at least one medication during pregnancy. Pregnant women will take an average of about 2.6 medications at any time during pregnancy with first trimester use of prescription drug increasing by more than 60 percent.

Use of four or more medications in the first trimester has actually tripled from about 10 percent to 28 percent. The source is listed below, but this encompasses a

year study. So only a small percentage of drugs are

contraindicated for use during pregnancy and lactation. These include drugs such as isotretinoin and mycophenolates. For most of the drugs, labeling should provide what is known in a way that will enable the prescriber to make decisions for treatment. The question is, how do we do this?

Let's take a look at a history of pregnancy and lactation labeling. So if we look

back into the 1960s you might remember the thalidomide teratogenicity and all the cases of fetal limb malformations that occurred in infants throughout Western Europe.

In November of 1960, Dr. Francis Kelsey of the FDA had refused to approve thalidomide in the United States, and as a result of this tragedy, in 1962 Congress enacted the Kefauver Harris Amendment to the Federal Food, Drug, and Cosmetic Act. Whereby, manufacturers had to prove that a drug was not only effective, but also safe. This led to several safety reports that emerged to report on this post-marketing information.

By the 1970s clinicians were faced with a vast increase in information that they had a hard time interpreting. So in 1979 the FDA introduced the pregnancy labeling category which provided standard regulatory statements. However, in 1994 several groups, including the Teratology Society, began to meet and recommended that the FDA delete these pregnancy categories from drug labeling, and instead replace them with narrative

statements that would summarize and interpret available data.

Between 1997 and 2003 several groups began to meet. There was expert input, advisory committees, focus groups all met to begin to decide how this rule would be written. In 2006 the physician labeling rule published. However, the pregnancy and lactation subsections of labeling that revision was deferred to a later date.

In 2008 the draft PLLR published, and that also followed a period of public comment from 2008 to 2013, and finally on December 4, 2014 the PLLR went into effect. Or it was published.

So what is the problem with the pregnancy letter categories? The pregnancy letter category system was seen as overly simplistic. It was seen as a grading system where A was seen as a drug that had minimal risk and X was seen as a drug that shouldn't be used.

In addition, a drug that had adverse reactions in animals was labeled as the same

category that had no animal information. Those were labeled Category C drugs.

So the intent of the PLLR is to provide the prescriber with relevant information for critical decision making when treating a pregnant or a lactating woman. More complete statements are made based on what is known of the risk. Considerations are made for medical and disease factors. Animal data is now put into context of human exposure. When there's human data available that is added into labeling, and when there are no data available that's explicitly stated.

So the PLLR went into effect on June 30 of 2015. All prescription drugs will be required to remove their pregnancy letter category by June of 2020, and this is a gradual process. Prescription drugs that are approved on or after June 30 of 2001 also have that additional requirement to change the content and formatting of labeling, and I'll provide you with examples of what this looks like.

In addition, PLLR reorganizes

information in prescription drug labeling to more clearly describe the data that are available, and to aid physicians and prescribers in the counseling of their patients who are using prescription drugs.

So let's look at an overview of the PLLR labeling changes. If you look on the left-hand side this is what labeling used to look like. You had Section 8.1 known as Pregnancy, 8.2 was Labor and Delivery, and 8.3 was Nursing Mothers. Now, what new labeling shows, and you can see on the right-hand side, 8.1 is still Pregnancy, but now Labor and Delivery forms a sub-heading under pregnancy.

8.2 is now known as Lactation, and the new section is Section 8.3 known as Females and Males of Reproductive Potential. This is the section that will include information about pregnancy, (inaudible), contraception, and fertility.

So let's look at each of the headings in a little bit more detail. Section 8.1, Pregnancy,

and there are four headings that would appear under that. First is pregnancy exposure registry. Then we have risk summary, and that's a required heading. Clinical considerations and then data.

So in a drug label that has information about a pregnancy exposure registry a following statement would appear. There is a pregnancy exposure registry that monitors outcomes in pregnant -- monitors pregnancy outcomes in women exposed to (trade name) during pregnancy. And then there is specific contact information, in particular, a phone number and website for the prescriber to call.

The risk summary, this is the required heading, if there is no drug systemic absorption then a statement such as this would appear in labeling. Mainly the (trade name) is not absorbed systemically following (whatever the route of administration) and maternal use is not expected to result in fetal exposure to the drug.

In drugs that do have systemic exposure the following will appear. If a drug is contra

indicated then this will appear first in the risk summary. This section will also have a risk statement based on human data. If there are no human data this will specifically be stated in this section. If there are human data the information will come from clinical trials, if there's a pregnancy exposure registry, other epidemiologic studies, or a well described case series. This information will be summarized in this section.

The risk statement on animal data will include specific information about the number and type of species that were studies, when the drug was given, what the animal doses were expressed in terms of human doses, and then what the outcomes were in the pregnant animals and their offspring. So the human data and the animal data risk statements are required.

Next is a risk statement based on pharmacology. This is included only in products where there is a well-understood mechanism of action. So we've included this in products --

oncology products, drugs that have cytotoxic potential. If you do include this statement there will be a cross reference to Section 12 where the prescriber can get more information.

The next required section here is the background risk information in the general population, and I'll provide you with an example on a later slide. But basically this provides the prescriber with what the background risk of miscarriage or malformations is in the general U.S. population. Then finally, if known, the background risk of a miscarriage or fetal malformations in the disease population.

So here's an example of labeling for a Section 8.1, Risk Summary, where there is a risk based on animal data. Now, as you can see in this case there really isn't a lot of information based on human data. But there is information based on animals. So this drug was given orally. It was given to pregnant rats and rabbits during the period of organogenesis, and then you note here the doses at which it was given, and then the

effects that were seen in the animals.

And then the last paragraph includes that background risk statement that I told you. What the estimated background risk is in the indicated population, and then the background risk of miscarriage and fetal malformations in the general population. These numbers come from the CDC and they've been stable for the past 30 years.

So turning our attention to the next heading, and this is known as Clinical Considerations. There are five optional headings that would be included only if the information is available. First is disease associated maternal and/or embryo fetal risk. We would include this section if there's any information that's related to the disease. For example, in a diabetes product, if a patient has uncontrolled diabetes what are the pregnancy complications that she faces? What are the risk to the fetus because of the diabetes?

The second heading is known as dose adjustments during pregnancy and the postpartum

period. This would be included if there were specific dose adjustments that need to occur in a pregnant woman. For example, certain anti-seizure medication or an antibiotic may have a dose change during pregnancy. If you include this section then it would be a cross reference to Section 2.

Third is maternal adverse reactions, and you would include this if a drug has potential to cause an adverse reaction in a pregnant woman. The fourth section is fetal and neonatal adverse reactions. This includes effects that would be seen due to the drug on a fetus or a neonate. Finally, labor or delivery. This was the effects of the drug is taken during labor or delivery.

The final section under 8.1 is known as Data. This is where you would have a detailed description of the data that had originally been summarized up above in risk summary and in clinical considerations.

The applicant typically provides the agency with a comprehensive review of any relevant

published literature, a review of their pharmacovigilance database, and if there is a pregnancy exposure registry they would provide that information as well. This would help support the language that we use to update the sections of labeling.

There are two sections. You would have human data and animal data. Again, the human data would have a description of the studies, the type of study that was done, how many subjects were included, how long the study lasted, any exposure information and limitations of data. Then the animal data section would have specific information about the animal studies that were conducted.

Now, let's turn our attention to Section 8.2. This is known as Lactation. There are three headings under Lactation. First is risk summary. This is a required heading. Then clinical considerations and data. So let's briefly look at each of these headings.

So risk summary, if a drug does not have

known systemic absorption, as statements such as this would appear. Basically, the drug is not absorbed systemically by the mother following whatever route of administration, and breastfeeding is not expected to result in exposure of the infant to the (drug name).

If there is systemic exposure then several things need to be present. First we need to know, is the drug present in milk or not? If it is present, do we know what the concentration milk is? Do we have the actual or estimated infant daily dose? What are the effects of the drug on the breastfed infants? What are the effects of the drug on milk production? If unknown, this would also be stated.

Finally, a risk benefit statement would be included, and I'll provide you with examples here in the next two slides, what this would look like.

So this is an example of a drug that -- where the class is known to be present in human milk. So although there's no specific information

about this drug being present in milk, this is a monoclonal antibody, so we do know that they are present in human milk. So I'm going to point your attention to the last section here.

This is the risks benefits statement that would be included in a drug where it would be okay to use during breastfeeding. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for the (trade name) and any potential adverse effects on the breastfed child from the (trade name) or from the underlying maternal condition.

In a drug that does have safety concerns where you do not want the mother breastfeeding. This is what labeling would look like. I'll draw, again, your attention to the last sentence where the risk benefits statement is as follows. Because of the potential for serious adverse reactions, and you would include what those particular concerns are, advise patients that breastfeeding is not recommended during treatment

with (trade name).

Okay. The last two sections of lactation are included only if there's information, so they're not required. There's clinical considerations, and you would include this section if you have information on how to minimize exposure to the breastfed infant, or if you have any information for the prescriber on how to monitor for adverse reactions. This would be included here as well.

The next section is data, and this would be included only if you have information available. Again, we do required that the applicant provides the agency with a comprehensive review of published literature and their pharmacovigilance database so that we can update this section.

This section would describe any human clinical lactation studies and provide the data here. If there are no human data, if there are any animal lactation studies this information would be described here instead.

Okay. Finally, Section 8.3 is Females and Males of Reproductive Potential. This would be included if there are recommendations for pregnancy testing, contraception, or when animal and human data suggest that the drug might effect fertility. Those are the three headings listed.

What Section 8.3 is, is a dedicated labeling section that consolidates all of the information from other areas of labeling. So it moves recommendations for contraception and pregnancy testing from Section 8.1 and 13, moves it all up to 8.3. It moves human fertility study descriptions and infertility considerations from Section 13 to 8.3. Specific information about animal fertility study descriptions will still remain in Section 13, non-clinical toxicology.

Here's an example of labeling that ended up using all three of those headings: Pregnancy Testing, Contraception, and Infertility. In this case there is information for the prescriber to get a pregnancy test for their patients if they're going to be using the product. There is

information about contraception advising females of reproductive potential, to use effective contraception during use of the drug, and then for, in this case, it's two weeks after the last dose.

Then the infertility section there are concerns in animal studies that this drug has caused infertility in rats. So this information is relayed here that there is also potential for seeing infertility in humans.

So in summary, the PLLR implementation is a gradual process. It will take another two to four years to complete this. All prescription drug labeling will be required to remove the pregnancy letter categories. PLLR provides a clear communication of available data to assist the prescriber with critical decision making when treating a pregnant or a lactating woman. The PLLR also notes when there are no data available.

Again, an overview of the sections that we discussed, 8.1, Pregnancy, 8.2, Lactation, and 8.3 Females and Males of Reproductive Potential

with each of the headings underneath them. So, as a conclusion, the PLLR provides a more structured approach to labeling that helps provide a more clearly -- just clear description of available data that can be used to aid in the complex risk benefit discussion between the prescriber and their patient. It also includes required statements when data are not available.

Our hope is that all stakeholders will work together to proactively seek information to fill these gaps. Provide you with some resources if you would like more information. The PLLR website. We'll provide more information about the final rule. There's information about the pregnancy registry website, and this is run by the Office of Women's Health, so if there is more information about a pregnancy registry this is where you might find it.

Other resources, I have links to the draft guidance for the PLLR, the physician labeling rule, so you have all those resources to obtain more information. If you are looking to

find product labeling, drugs at FDA, DailyMed, Lactmed, and CDC are all good sources.

This concludes my presentation. Are there any questions?

DR. HUDAK: Just one general question that's -- I'm sorry, I won't take -- you go first then.

DR. CUNNINGHAM: Melody Cunningham. Just sort of a reminder question, but when we look on 8.3 the animal fertility study descriptions remain in Section 13. Kind of reminder point, but I'm wondering why those remained in 13 and the others were moved up?

DR. DINATALE: We thought it would probably be better to keep the animal data in that section, you know, Section 13, and to describe more of the human effects in Section 8.3. There's usually like a brief statement, you know, that says, you know, because of animal studies, you know, women might -- there might be infertility noted, and then there's a cross reference, you know, see Section 13.1 for more details.

DR. HUDAK: So I think I recognize this has been a work that's taken a long time, and there have been a lot of constituencies that have contributed. I think this is really valuable. You know, as caretakers, you know, for mothers and babies we are very often confronted with the need to have good information on drug effects on mothers and babies.

Hopefully this will allow better integration and congruency among all the different resources we have because right now, as you know, there are sometimes some significant nuances, different nuances, between different sources on particular drugs or agents.

DR. DINATALE: Right.

DR. TURER: I have a question regarding the maternal registry. I wondered to what extent it would be possible to have a registry that went into the children that were exposed in utero. Because my concern is that we're going to capture the data through labor and delivery and that's where it's going to end. But to understand the

longitudinal impact would be really beneficial to connect what are the child outcomes of children who were exposed?

DR. DINATALE: Right. And a lot of the pregnancy registries, it depends. Some of them will follow them for 12 months, some of them will follow then two years, three years. I haven't seen anything that's gone beyond 3 years in the ones, at least, that I reviewed. But definitely, you know, some good points for particular drugs that might have longer effects.

UNIDENTIFIED MALE: Just to comment on that though, but at the same time we're not typically -- with a pregnancy registry, talking about things that end at labor and delivery and don't follow on with what happens to the infant in terms of any outcomes.

DR. DINATALE: Right. Usually there's a pediatrician that will evaluate the child. There are certain -- you know, sometimes they'll follow them maybe every month, every three months, depending on the pregnancy registry. There's a

set number of months that they follow them, you know, usually up to 12 months, but sometimes even longer. So there is a pediatrician that is evaluating them and providing feedback to the registry.

DR. HUDAK: Dr. Havens?

DR. HAVENS: Dr. Havens. You're not requiring the establishment of a registry for every drug?

DR. DINATALE: Right. No, it's not every drug.

DR. HAVENS: Nor are you requiring that people enter their patients' children, perhaps, into the registry? That's not required by this rule?

DR. DINATALE: Right. No, it's not a requirement. Yes. I mean, there are certain drugs, you know, certain classes like, for example, anti-seizure medications where there are registries. So if a new anti-seizure medication comes out they get entered into a registry and they get followed.

It's not a requirement. I mean, our hope is that our provider will read the labeling, will see the information, and will kind of be proactive. You know?

DR. HAVENS: I just want to compliment you on a great discussion of this complex rule. The rules is great and I appreciate your discussion of it.

DR. DINATALE: You're welcome.

DR. HUDAK: Dr. Moon?

DR. MOON: Oh.

DR. HUDAK: You were signaling. Very good.

DR. JONES: I just had a question. So how are you going to roll this out to the public and to medical providers because this is a great change, but it's going to be a significant change. So how are you going to work with medical providers to make sure they understand the new label?

DR. DINATALE: So over the past couple of months we have been, either myself, a lot of

members of the maternal health team have been out and speaking at difference conferences. You know, so we've been working with the Office of Women's Health. Either we're providing - - we're speaking at these conferences or being available there at a booth to answer questions. So that's one way.

Let's see, other ways. I know the Office of Women's Health has also worked on providing information to kind of get it out to, you know, to the general public as well. So we are working on advertising it and, you know, letting people know about it.

DR. SHWAYDER: Dr. Dinatale, that was great, and I'd like to bring this back to Henry Ford Hospital. Is this PowerPoint available?

DR. DINATALE: I think it is, yes.

DR. NELSON: It's on the website as a PDF which you can use, and no government work is copyrighted.

DR. HUDAK: Dr. White, I think had a question.

DR. WHITE: Thank you very much. This

will help us in fetal cardiac evaluations tremendously to be able to tell the parents what to expect from their exposure early. And as an aside, this is another place where understanding the pharmacogenetics will make a big difference as evidenced by the studies with codeine and codeine toxicity where the CYP 2D6.

DR. HUDAK: Okay. I think that's good. Thanks very much for that presentation.

DR. DINATALE: Thank you.

DR. HUDAK: So I want to assure everybody that we've done tremendous work here this morning. We're back on the secret schedule which now calls for lunch with everybody to regroup at 1:00.

(Recess)

DR. HUDAK: Back into session. Marieann has a couple of administrative announcements.

DR. BRILL: With the fiscal year ending your travel reimbursements will not be posted until November of this year. So if you have questions please contact Euneka Joseph. Sorry

about that.

DR. HUDAK: Okay. Glad I didn't have to make that announcement. All right. So we'll start the afternoon session. We have some new people from FDA at the table to support Dr. Taylor, so maybe you can introduce yourselves?

DR. BRINKER: Hi. My name is Allen Brinker and I'm a medical officer in DPV, and I'm here today in support of colleagues who couldn't be here today because they are at the Chantix AC. So I'm representing the review team that looked over these in the post-marketing setting.

DR. BAZINI: Hi. I'm Alla Bazini. I'm one of the medical officers in the Division of Anesthesia, Analgesia and Addiction products.

DR. CRISAFI: Hi. I'm Leah Crisafi. I'm the team leader for the nesthesia team in Division of Anesthesia, Analgesia, Addiction products.

DR. PHAM: Hi. My name is Tracy Pham. I'm a drug use analyst from the Division of Epidemiology 2, Office of Surveillance and

Epidemiology.

DR. HUDAK: Okay. Very good. Dr. Taylor, you've got a triple header here.

DR. TAYLOR: Yes.

DR. HUDAK: Okay. Say a few words about yourself and then you can get started.

DR. TAYLOR: Hi. I'm Dr. Amy Taylor and I'm a medical officer in the Division of Pediatric and Maternal Health in CDER at FDA. I'll be presenting first the Bloxiverz pediatric focused safety review.

This is the outline of my presentation. I will start with background information on the product. Bloxiverz or neostigmine methylsufate is a cholinesterase inhibitor approved for marketing on May 31, 2013. Neostigmine has been marketed as an unapproved product since 1939.

Bloxiverz is indicated for the reversal of the effects of non-polarizing, neuromuscular blocking agents after surgery for all age groups. Bloxiverz is contraindicated for known hypersensitivity, and in cases of peritonitis or

mechanical obstruction of the intestines or urinary tract.

There are five warnings and precautions which you see here. Next I will touch on the clinical studies which supported their approval of Bloxiverz. The evidence for efficacy is derived from published literature. The clinical studies include randomized spontaneous recovery or placebo controlled studies. A total of 404 adult patients and 80 pediatric patients were studied. Patients had reductions in their recovery time from neuromuscular blockade compared to spontaneous recovery.

I will now discuss the drug use trends. Over the cumulative time period from May 2013 through December 2015 nearly 654,000 pediatric patients age 0 to 16 years had an inpatient or outpatient hospital discharge billing for neostigmine injectable products from U.S. non-federal hospitals. This number translates to 4 percent of the total

million patients who were on neostigmine

injectable products.

There are limitations to the drug use database which are presented here. Data from children's and other stand-alones, especially hospitals, federal hospitals, and VA facilities are excluded in the drug use analysis.

I will now discuss the FAERS safety data. A search of the FAERS system from May 31, 2013 to March 29, 2016 revealed five pediatric reports, all of which were coded as serious. There were no deaths. All of the reports were reviewed. One reports was excluded from the case series because it was a duplicate and one was excluded because it was a report of a transplacental exposure.

This leaves us with a case series of three cases. The next few slide will present the cases in the case series. The first is of a 1 year old male undergoing a diagnostic laparoscopic exam, was diagnosed with pulmonary edema after administration of neostigmine. This delayed his extubating and he remained in the hospital for two

days.

The second case is also a 1 year old male undergoing vitrectomy and lens reconstruction. He was diagnosed with pulmonary edema after neostigmine administration. He recovered.

The third case is a 9 year old male undergoing tonsillectomy. He demonstrated signs of pulmonary edema after neostigmine administration leading to re-intubation. After his condition improved he was again given neostigmine and, again, experienced signs of pulmonary edema. After treatment with aminophylline, chlorpheniramine, and theophylline he recovered.

A search of the FAERS system prior to May 31, 2013 was conducted. Two additional pediatric cases were found. The first case is a 16 year old man with Brugada Syndrome undergoing implantation of a cardioverter defibrillator. He developed signs of pulmonary edema after neostigmine was administered. He recovered with

treatment.

The second case is a 6 year old male undergoing corneal repair. He developed signs of pulmonary edema after neostigmine administration and extubating. He was reintubated and recovered after treatment.

In the five cases presented a temporal relationship between neostigmine and pulmonary edema was seen. However, all five cases were confounded by potential airway management difficulties, and two cases were confounded by prior respiratory or cardiac issues. In addition, we identified two literature reports of non-cardiac pulmonary edema in adults post-neostigmine administration.

This concludes the pediatric focus safety review of FAERS reports. There are reports of pulmonary edema after administration of neostigmine. Due to the rarity of reports and confounding, FDA will continue routine, ongoing post-marketing safety monitoring. Does the committee concur?

I'd like to thank these folks for their help with my presentation.

DR. HUDAK: Okay. Thank you, Dr. Taylor. So this is open for discussion. Yes, Dr. Hoehn?

DR. HOEHN: It seems really hard to tease out what would be sort of post-obstructive pulmonary edema from an extubating related event. So I didn't know if you had any data on the incidence of pulmonary edema post-extubating without neostigmine?

DR. TAYLOR: I don't know if the division has that information or if OSE?

DR. BRINGER: I'm looking at my colleagues here and they're shaking their heads, but we, as a group, have access back at White Oak where we work to more resources, including some pediatric intensivists. We discussed each of these cases with them, and they say that they see this. This is not a truly remarkable event. That you do see this from time to time.

I would also want to point out that

these cases have occurred -- have come to us over some time, and some of them, most of them, all of them are outside the U.S. And so we can't necessarily know how these kids were treated and what conditions were going on with concern or in comparison to what's contemporary American medicine.

So getting to the point, my colleague with whom we discussed this felt like none of these cases it was -- you could show -- you could consider without a reasonable doubt that this was neostigmine.

DR. HOEHN: Just a clarifying question, so none of those cases were in the U.S.? They were all international cases?

DR. BRINKER: Yes.

DR. HOEHN: Okay. I have no concern, whatsoever, about neostigmine. That's why I think it's likely something else. That's why I just didn't know if there were comparisons made to what the incidence was with neostigmine. Okay.

DR. HUDAK: So I don't know if this helps or not, but in the final review on Page 16

it does say that noncardiogenic pulmonary edema can be a consequence undergoing anesthesia. That advanced airway incidences is estimated to be 0.1 percent.

I was curious looking at the -- your summation that there were confounding potential airway management issues. That didn't quite align with the individual detail or sort of reports that were given for each of these cases. So I don't know what additional information you had to conclude that?

The one case where there was the reintroduction, the reoccurrence of the pulmonary edema was very striking.

DR. BRINKER: So I can't speak for my colleague who's not here today. We tried to provide you with a synopsis that worked well on a PowerPoint slide, and we discussed each one of these cases with all the data that was available to us, individually, when we worked up these cases.

DR. HAUSMAN: Hi. Ethan Hausman. I

just pulled up an article, literature review from 2012, Annals Medical Health Science Research, and the incidence overall in an unselected population is 0.1 percent after general anesthesia. However, if there's an underlying background of obstruction the incidents can range from about 9.5 percent to 12 percent, in this article.

DR. HUDAK: Dr. White?

DR. WHITE: It was striking to me that we don't capture use data from pediatric hospitals for neostigmine? So do you have any estimate of how many additional cases of neostigmine might have been given if you included children's hospitals? Is there any way to even estimate that number?

DR. TAYLOR: Dr. Pham?

DR. PHAM: So for the drug use data any data from

(inaudible), children hospitals, or from federal facilities we don't capture that. But if there's -- if a hospital has a center, a

children's center, that might be captured in our data. But we wouldn't be able to obtain any of the adverse event coming from the data -- based on the data that's available to us.

DR. WHITE: Well, you get the adverse events. You just wouldn't get the incidents of the use of neostigmine because this is the drug utilization database that excludes that data. I'm just curious if we have any idea of how many surgical case are preformed? Any way of estimating how many likely cases of neostigmine use there might be in pediatric hospitals compared to other hospitals.

I imagine most children in the country that are being treated surgically are not being treated surgically in children's hospitals, but that -- it's a major piece of data that would help us determine is this a high incidence of side effects above and beyond what would be 0.01 or is it much, much lower? I mean, I know it's a

difficulty.

DR. NELSON: This data is not a denominator for the numerator, and so it'll be higher, but I don't know if it necessarily lends itself to any different interpretation. We don't have database -- I mean, part of it to contact the databases -- you know, that's just the nature of the databases.

UNIDENTIFIED MALE: Yes. Typically we don't have access to precise patient-level data.

DR. BRINKER: So there are a lot of limitations with spontaneous FAERS data, especially for an old drug like this, but the numerator here, for the -- the domestic enumerator is 0.

DR. HUDAK: Yes, okay.

DR. FISCHER: Gwen Fischer. I just want to point out that at least two of these cases had other things going on in the case that very much increased the risk of

(inaudible). One being laryngeal spasm and the other being

tonsillectomy which is one of the most common pediatric procedures for kids being intubated and getting use of these drugs. So it seems like very confounding data to me.

DR. HUDAK: Very?

DR. FISCHER: Confounding data.

DR. NELSON: I'll just make a comment too. The reason we brought this is not so much because we think we can make a lot of the pulmonary edema, but because we thought it was remarkable, A, that there was this, but, B, wanted to alert the committee that there are drugs out there that are marketed unapproved drugs, and here's one from 1939.

And so you've got however many years that is. I mean, that goes back to when the Food, Drug, and Cosmetic Act was first passed because of, you know, we thought that was remarkable enough, even with just three events, all foreign with zero U.S. to just let you see it as a group.

DR. HUDAK: Any other thoughts or comments before we vote on the question? So we will vote on the question of the FDA's recommendation to continue their post-marketing safety monitoring and not do anything further this time about pulmonary edema in terms of label.

So vote on your speaker. Okay. That's a nice slate, so we'll go around the room starting with Dr. Anne.

DR. ANNE: Premchand Anne. I concur.

DR. WADE: Kelly Wade. I concur.

DR. WHITE: Michael White. I agree.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CNAAN: Avital Cnaan. I concur.

DR. SHWAYDER: Shwayder. Yes.

DR. TURER: Christy Turer. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. SAVEL: Wael Savel. I concur.

DR. MOON: Mark Moon. I concur.

DR. FISCHER: Gwen Fischer. I concur.

DR. HUDAK: Okay. So the summary is that the committee unanimously supports the FDA recommendation on this medication neostigmine.

So going on to your second header, doxycycline, which has been in the news because of an increase in the cost of pill from 3 cents to over $5 in some places. Another issue entirely, but happy to hear about the data.

DR. TAYLOR: Again, this is an outline of my presentation and I'll start with background information.

Doryx or doxycycline hyclate is a tetracycline antimicrobial approved for marketing on May 6, 2005. Doryx has multiple indications which are listed here. Doryx is approved for use in pediatric patients. However, it should be used in patients 8 years or less only when the potential benefits are expected to outweigh the

risks due to the effect on tooth development and growth.

Doryx is contraindicated for known hypersensitivity to tetracyclines. There are six selected warnings and precautions which I've shown here. I will now discuss the drug use trends.

This table displays the nationally estimated number of patients with a dispensed prescription, oral doxycycline hyclate stratified by age, dispensed from U.S. outpatient retail pharmacies from April 1, 2013 through December 31, 2015. Pediatric patients age 0 to 16 years accounted for 6 percent of the total, or approximately 1.2 million patients.

I will now discuss the FAERS safety database. A search of the FAERS system from January 1, 2006 to December 31, 2015 reveled 30 pediatric reports of which 23 were coded as serious. There was one death. All of the reports were reviewed. One report was excluded from the case series because it was a duplicate. This leaves us with a case series of 22 cases,

including one death.

Of note, all of the cases were in patients aged 12 to 17 years. Most were taking doxycycline hyclate for acne.

This slide presents the pediatric adverse events which included the suicide of a 13 year old by gunshot. In addition, there were two cases of suicide attempt, one case of anxiety, and one case of anxiety and depression.

Given the low number of cases relative to time and extensive use the prevalence of anxiety, depression, and suicide in adolescents, and the potential for acne to contribute to psychiatric conditions such as depression, an association of these events with doxycycline is unlikely.

This slide is meant to remind us of the epidemiology of youth suicide. There are approximately 4,600 youth suicides each year, and it is the third leading cause of death among youth aged 10 to 24 years.

This slide lists the other series

nonfatal adverse events reported, including intracranial hypertension which is listed in Warnings and Precautions. Please note, a case may have more than one event.

This concludes the pediatric focused safety review of FAERS reports. There were no new safety signals identified. FDA recommends continuing routine ongoing post-marketing safety monitoring. Does the committee concur? And I would like to thank these people for the help with my presentation.

DR. HUDAK: Okay. Open for discussion. Dr. Havens?

DR. HAVENS: Peter Havens. Just to point out that I really appreciate having been able to read these statistical evaluation in the background which shows the extent to which FDA is willing to work really hard to make sure that the data upon which they base their recommendations are adequate. Whoever did that job gets the prize.

DR. SHWAYDER: Tor Shwayder here. I

write for doxycycline probably eight times or 20 times a day because we use it since tetracycline went off the market. I'd like to know if the data reflect the doxycycline monohydrate or does it just reflect the hyclate? Because I write for whatever the pharmacy will fill.

DR. TAYLOR: Yeah. Oh, actually, I'll let --

DR. READY: Travis Ready, drug use, Division of Epidemiology. We only looked at the hyclate salt.

DR. SHWAYDER: Do you expect any difference in the monohydrate?

DR. READY: I would not expect any difference. I'm not sure if I fully understand your question though. Are you specifically just thinking about the utilization as compared to the hyclate?

DR. SHWAYDER: Yes. I write for them randomly because the insurance one day will pick one and not the other depending on the cost. So I write on my prescription, one or the other,

tablets or capsules, don't call me for prior authorization just fill it. Period. So however it gets filled it gets filled.

DR. READY: Okay. I would defer back to my colleagues because Doryx was what triggered the PAC meeting, so therefore, we broadened the base to include generic Doryx or doxycycline hyclate.

DR. SHWAYDER: Thank you.

DR. HUDAK: Dr. Dracker has a question.

DR. DRACKER: I just want to make a comment. I wish the committee could deal with the issue of availability and pricing like we've eluded to. Because those have been the two biggest issues with this drug, is trying to find it and trying to get it paid for.

DR. HUDAK: Yes. Apparently, the Lyme disease prone people up in Cape Cod, pharmacists up there have as hard time getting adequate supply, so. Anyway, so I think we're open for a vote on this. We will start with Dr. Anne again.

Oh, do we have another question? I'm sorry.

DR. SAVEJ: Is esophageal ulcers listed as an adverse reaction on the label of the drug or no?

DR. TAYLOR: Yes, it it.

DR. SAVEJ: Is it, okay.

DR. HUDAK: Okay. So we will --

DR. WADE: I have got --

DR. HUDAK: Dr. Wade.

DR. WADE: Sorry. Kelly Wade. I just wanted some guidance on how to think about these cases of suicide where there rarely is a direct causality, you know, link, but in the review there was concerns expressed by a parent of causality, and in the case that, you know, ended in death there was an 11 month time period, but in the other cases there was a shorter time period.

But in general, I think, these suicide issues related to drugs or whether or not they can be is in the press and is at the forefront, so how -- can you give us some guidance on how to think about the drug related effects specifically regarding suicide?

DR. LEVIN: Bob Levin from Pharmacovigilance. Yes, it's one of the most severe type of events, obviously, so in some case -- well, overall, it's a thing we do struggle with and we have several ongoing project to sort out, at a best, try to assess causality, but how to interpret the numbers too. What kind of studies you need? So completing suicide is, obviously, quite rare, and to really have a fully powered study to detect a difference you'd really need tens of thousands of patients. So it makes it really tricky to study it.

We do know, in general, it's surprisingly common how, at least suicidal ideation and thoughts and non-self-injurious behavior without the intent for suicide is quite common through the pediatric age range. Obviously, completed suicide is much more rare.

To look at your question broadly, like I think, you're asking and pointing out. We agree. It's one of the most serious adverse events to try and disentangle what's causal, what's not. And as

far as spontaneous reports, one of the main factors in whether a report is submitted is whether it's a serious adverse event. So it's hard to interpret exactly. There's a lot of missing information from these cases.

Typically, I'm thinking of all sorts of drugs for both adults and pediatric patients in which suicide might be a risk or a potential risk, it's really hard to sort out, as you might guess, but we're trying. Generally, not just psychiatric trials, but a lot of trials with different indications are including perspective assessments of suicidality, so that's one thing we're trying to do with drug development. It's a really difficult area, but we're trying to figure out different types of study designs and post-marketing data collection that can get to that.

DR. HUDAK: Dr. Nelson?

DR. NELSON: Just to expand on that last point, you know, Bob will probably remember, but now, I guess over a dozen years ago, when the

question of suicidality came up with SSRIs and the like that was all controlled clinical trial data, and even to interpret that controlled clinical trial data there was a adjudication of all the cases done by Columbia and then the development of a Columbia suicidality scale.

Specifically, unless someone else develops a new scale that scale is being incorporated into all ongoing clinical trials where there's a concern about the ability to monitor the potential for a suicidality signal which includes most psychotropic, includes a lot of the neurological drugs, and the Division of Neurology Products and the likes.

So going forward, I think there is a way, but out of these kind of data very difficult. It was even difficult to do it in those pediatric data which were, I think, on the order of 14 or 15 controlled clinical trials that were randomized and placebo controlled, and you still needed to go back and adjudicate that in order to be able to ascertain whether there was or was not a signal.

So going forward I think there's an answer. But going back to these kind of data, as Bob pointed out, is very difficult to sort out.

DR. HUDAK: I think it is difficult. I think I'd point out that, you know, among adolescents, if you take adolescents from 12 to 17 there are probably about 25 million adolescents in the United States, and through incidences, if you have 4,600 suicides in this age group that's 1 per 5,000 adolescents, so there is, you know, going to be an expectation there's going to be suicides in a drug that's used widely.

DR. WADE: Kelly Wade again. Is it or when is it or is it ever reasonable to pull in case reports from the literature or case series? Just because there are mood swings and side effects in this drug class. So when do you invoke literature review?

DR. TAYLOR: Really, it's our routine to do that. We search the literature, almost automatically, with each signal or potential risk that we work up. So that's a common practice that

we use.

DR. HUDAK: Kelly, we had one presentation this morning, I can't remember which drug it was, but the information they presented did include some literature reports. So they typically do that when they go through their adverse event analysis.

DR. WADE: Yes. I just didn't see that in this case, and just doing simple searches quickly it looks like there is some literature in this domain.

DR. READY: You mean suicidality in general? Yes, there's a --

DR. WADE: And doxycycline.

DR. READY: Okay. Yes, I'm not aware of the specific literature for that, but that's a good point. Yes, there's more and more literature all the time about suicidal ideation and injurious behavior and whether it's drug-related.

DR. HUDAK: Dr. Cope, do you have?

DR. COPE: Yes. I just wanted to say we're all involved, the different teams, you know,

in the review. And, like, for example, there was an article I found out of UK that was doxycycline suicidality but, again, these are adolescents. And, you know, I mean, at least when I did 10 years in clinical practice seeing teenagers, I mean, sometimes the depressed ones are the ones that come in for, you know, acne therapy. You know? Or the ones that are being treated for chlamydia have, you know, other sorts of problems going on.

So many times the case reports will see or actually be the ones that end up in our reviews, sometimes. So.

DR. READY: Another difficult area. It's especially difficult with severe skin disorders. There's no question there's a greatly, highly increased risk of all psychiatric events, including suicide. So it makes it even more difficult to try to sort our causal factors.

DR. WADE: I think I was just thinking that in these cases of teenage suicide, you know, maybe this is an area where just a short summary

of what's in the literature in case reviews would just add to the comprehensiveness of the data put before us, even though we all recognize there are case reports. Would just add to the thoroughness.

DR. HUDAK: Okay. Thank you. So I think maybe it's time to vote. So, Dr. Anne, want to start with you?

So the question is do we agree with the FDA's recommendation to continue their post-marketing safety studies and not alter the label.

DR. ANNE: Maybe should we do the buttons first or?

DR. HUDAK: Oh, I'm sorry. Do the buttons first. Okay. Now we can go around the room.

DR. ANNE: Premchand Anne. I concur.

DR. WADE: Kelly Wade. I concur.

DR. WHITE: Michael White. I agree.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I

concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CNAAN: Avital Cnaan. I concur.

DR. SHWAYDER: Shwayder. Concur.

DR. TURER: Christy Turer. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. SAVEJ: Wael Savej. I concur.

DR. MOON: Mark Moon. I concur.

DR. FISCHER: Gwen Fischer. I concur.

DR. HUDAK: Okay. Excellent. Another unanimous with the recommendation for continue post-marketing surveillance.

The last one in your triple header. Is there anybody else coming to the table for FDA? Welcome.

DR. STARKE: I'm Peter Starke. I'm medical officer and associate director for labeling in the Division of Pulmonary Allergy and Rheumatology.

MS. Kalra: Dipti Kalra. Division of

Pharmacovigilance.

DR. PHAM: Tracy Pham, drug use analyst, Division of Epidemiology, OSE.

DR. BRINKER: And Allen Brinker, medical officer DPV.

DR. HUDAK: Okay. Very good, Dr. Taylor?

DR. TAYLOR: So, again, an outline of my presentation starting with the background information on the product. Xolair (omalizumab) is an anti-IgE antibody originally approved for marketing on June 20, 2003. Xolair is indicated for the treatment of moderate to severe persistent asthma in patients 6 years and older, and for chronic idiopathic urticarial disease in adults and adolescents 12 years of age and older.

Xolair is contraindicated for known hypersensitivity. I've listed six of the warnings and precautions from the labeling.

Next I will touch on the clinical studies and subsequent labeling changes with initiated this PAC review. The safety and

effectiveness of Xolair for the treatment of chronic idiopathic urticarial was evaluated in 39 patients
to 17 years as part of two larger studies, with a total of 640 adult and adolescent patients.

The CIU indication was added to the labeling, along with instructions for administration of Xolair for CIU. Information on adverse reactions was also added to Section 6 of the labeling. Information on the clinical studies in pediatric patients with CIU was added, as well as a rationale for not studying patients less than 12 years of age. You can see that there at the bottom of the slide.

However, the statement was subsequently removed in July of this year after completion of studies in patients 6 to 11 -- sorry, 6 to less than 12 years with asthma. This approval of Xolair for the younger age group was supported by negative results in the Xolair's long-term study that did not show an imbalance of malignancies in

patients 12 years of age and older who are being treated with Xolair.

Information on the clinical studies for CIU was added to Section 14.2. I'll not discuss the drug use trends.

Because Xolair was mainly distributed to mail order specialty pharmacies and clinics, we examined Xolair utilization patterns based on a sample of U.S. outpatient retail, mail order, specialty, and non-retail settings. Over the cumulative time period from March 20, 2014 through February 2016 nearly 4,000 pediatric patients aged 0 to 16 years had a Xolair prescription or medical claim.

Of these, the majority of Xolair use was among patients aged 12 to 16 years. Although the data suggests that there may be use in patients under 12 years of age this cannot be validated due to the lack of assess to patient medical records.

These are the limitations to the Xolair drug utilization analysis. I'll now discuss the FAERS safety data.

A search of the FAERS system from August 1, 2011 to July 31, 2016 revealed 420 pediatric reports of which 405 were coded as serious. There were nine deaths. There were three additional reports of pediatric deaths identified among reports not reporting in age.

So we now have a total of 408 pediatric reports with a serious outcome. All of the reports were review, 285 reports, including five deaths were reviewed and excluded for the reasons you see here. This leaves us with a pediatric case series of 123 cases, including seven deaths.

This slide lists the causes of death for the seven cases with a fatal outcome. The following factors alone or in combination, negatively affected causality assessment, insufficient clinical information, underlying contributive disease, concomitant medications, and lack of temporal relationship between omalizumab administration and the event.

Of the 116 remaining cases which describe serious, nonfatal, unlabeled adverse

events, 92 has alternative, plausible explanations for the events, such as you see listed here.

Of the remaining 24 cases, 19 reported adverse events classified under infections and infestations. Two cases with adverse events were classified under investigation. One case of Stevens-Johnson Syndrome, one case of secondary adrenocortical insufficiency, and one case of pain in extremity.

This concludes the pediatric focus safety review of FAERS reports. No new safety signals were identified. FDA recommends continued, routine, ongoing post-marketing safety monitoring. Does the committee concur? And I wish to thank the following folks.

DR. HUDAK: Okay. Thank you, Dr. Taylor. This is now open for discussion. Dr. Shwayder?

DR. SHWAYDER: So I see hyper-IG people all the time. Mainly in the gaze of very bad eczema, doc aid or stat-3 mutations. And beg, we beg for omalizumab and we're always refused. So

(inaudible) of this particular committee, but some way or another we've got to let the FDA know that we need this medicine. Because I can count on one hand the number of common idiopathic urticarial I've seen in years, but I see these others every day.

DR. HUDAK: Dr. Cnaan?

DR. CNAAN: You have this study that you reported about in the 6 to 12 years old where my understanding was that it had negative results, is that correct?

DR. TAYLOR: No. I'll defer to Dr. Stark, but I don't believe it was negative.

DR. STARKE: So this is Dr. Starke. So the pediatric indication for use in asthma was added in July of this year. We're talking about 6 through 11 years of age. Previously it was approved for both indications, asthma and CIU down to 12.

The reason that we allowed the indication, you may recall that there was an advisory committee back in 2009 that discussed the

pediatric studies to support and asthma indication in 6 through 11 years of age. I presented at that advisory committee. I was the primary reviewer. The studies did support the indication, at the time. But at the time we had a concern about malignancy risk that had yet to be fully explored that had shown up in the original adult and adolescent clinical trials.

So the company was in the process, at that time, and since completed a very large, five year observational cohort study called XLs that included approximately 5,000 patients treated with Xolair and 2,500 patients not treated with Xolair. And on the basis of the results of that study we felt that it would be reasonable to reconsider the indication for the 6 though 11 years of age, and the company resubmitted, and we approved it. I hope that explains it.

DR. CNAAN: Yes. Thank you. I guess I was asking not so much about the asthma, but the urticarial. There was no study in urticarial in 6 to 12?

DR. STARKE: Not that I'm aware of, no.

DR. TURER: I agree. I was not clear when reviewing the data given to us if we were being asked to comment on it as an indication for CIU. So I wanted to understand better. Are we being asked to give an approval of omalizumab for CIU? Okay. Because I didn't have the data to make that -- thanks.

DR. STARKE: This is Dr. Starke. I would add that we would probably, at this point, reconsider if the company wanted to do or provide the data for the 6 through 11 years of age for CIU.

DR. NELSON: Mark, given there's many new members, so this committee is reviewing, sort of a pediatric focus post-marketing safety which is triggered by labeling changes, and so you will see often when there's multiple label changes things come back. But if there was a question of approval on the table that would be the division-specific pulmonary and allergy committee supplemented, perhaps, with pediatric experts.

Although there are some pediatric experts.

So this committee does not get asked those questions. We didn't appreciate the extent to which that might be confusing from the document.

DR. HUDAK: Okay. I think we're ready to go around. So we'll start, Dr. Fischer. Oh, buttons first. Buttons first.

Okay. Now we can go around the table.

DR. FISCHER: Gwen Fischer. I concur.

DR. MOON: Mark Moon. I concur.

DR. SAVEJ: Wael Savej. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. TURER: Christy Turer. I concur.

DR. SHWAYDER: Shwayder. Concur.

DR. CNAAN: Avital Cnann. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. I agree.

DR. WADE: Kelly Wade. I concur.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: Very good. So another unanimous agreement with the FDA recommendation for Xolair.

All right. Our final drug for the day -- oh, okay, so we do have one recusal and who's that?

DR. BRILL: Dr. Jones will be recused from the discussions of Karbinal.

DR. HUDAK: Okay. So Dr. Hausman, do you have anybody coming to the table in your support?

DR. HAUSMAN: We still have Dr. Starke and --

DR. STARKE: I'm Dr. Starke.

DR. HUDAK: Dr. Starke.

DR. STARKE: Allergy, Rheumatology. I'm associate director for labeling and medical officer, and I was the primary medical officer for

the carbinoxamine safety issues back in 2007 or '08, but not for the Karbinal. But I'm here representing.

DR. NGUYEN: Annie Nguyen, safety evaluator for the Division of Pharmacovigilance.

DR. LEE: Joann Lee, drug use analyst, Division of Epidemiology.

DR. HUDAK: Okay. Welcome, so Dr. Hausman?

DR. HAUSMAN: Good afternoon. This session will be about Karbinal ER and we can see the outline that we'll be following today. As noted on the slide, Karbinal ER is an extended release oral suspension H1 histamine receptor antagonist first approved in 2013. The 2013 approval prompted the current post-marketing drug use safety review and today's presentation.

I may refer to carbinoxamine products generally as CM and Karbinal ER and KER. As noted on Slide 4, Karbinal ER is indicated for several allergic indications including seasonal and perineal allergic rhinitis. It's also indicated

as an adjunct to epinephrine and other measures in the treatment of acute anaphylaxis, and as a treatment for allergic complications occasionally reported with receipt of blood and plasma exposures.

So from the regulatory history, in the 1950s Clistin was first approved as a single active ingredient carbinoxamine product of treatment of allergy indications in patients 1 year of age and older. In the 1960s, carbinoxamine alone or in combination with other active ingredients was subsequently marketed for a variety of unapproved indications, including, but not limited to treatment of colds and coughs, and these are indications for which carbinoxamine was never approved. As well as some other allergic symptoms in infants and young children, as well as in older patients.

So in the 1980s and 90s marketing applications for Clistin tablets and elixir were withdrawn. However, this is not because of issues related to efficacy or safety of the drug. So in

the early 2000s generic marketing applications for single ingredient carbinoxamine tablets and solutions were approved based on the agency's prior findings of efficacy and safety from Clistin.

In 2005 - 2006 period, FDA noted a safety signal of death with the use of carbinoxamine containing drug products in children under the age of 2 years. We'll be discussing this further on the next slide or two.

So the summary of the safety review and actions. So from 1983 through 2006 there are 21 deaths reported in children younger than 2 years of age. On investigation of the reports, a relationship of those deaths to carbinoxamine was not established. Most or all the deaths were associated with the use of unapproved combination products containing carbinoxamine along with pseudoephedrine.

So for the actions, at that time, the action for the approved single active ingredient carbinoxamine products was to put a

contraindication for use in labeling for children less than 2 years of age, and removal of dosing information from labeling for children 1 to less than 2 years of age. The actions for all unapproved carbinoxamine products was removal from marketing.

So the basis of approval for Karbinal ER is listed up on the slide. Safety and efficacy of Karbinal ER in patients over 2 years of age is based on demonstration of bioequivalent to the immediate release reference product. This is reflected in Sections 6, 12.3, and 14.1 of the label that you have in your background package.

PREA studies for patients less than 2 years of age were waived because there is the conclusion that there was evidence that suggested that there would be a safety issue in that group. So representative sections of labeling on presented on this slide. There's the contraindication. There's also a contraindication for use in nursing mothers because of a risk of potential mortality in their infants.

Please note under Section 5, Warnings and Precautions, the second bullet which is 5.5, use of accurate measuring devices. This is specifically noted in labeling, teaspoons are not accurate. If anybody in the greater D.C. area has been listening to the radio the last couple days, it's my understanding that the American Academy of Pediatrics is banging this drum again. It's a very important issue.

So in Section 8.4 this reflects that the deaths that have been reported in patients 2 years of age and younger who were taking carbinoxamine containing products. And it highlights, again, the contraindication I those patients.

We now go to the drug utilization slide and I lost my place, so excuse me for one second. So this graph displays the total number of pediatric patients 0 through 16 years of age who received the dispensed prescription of Karbinal carbinoxamine ER from U.S. retail pharmacies from March 1, 2013, which is the approval, to February 29, 2016. Pediatric patients from 0 to 16 years

of age accounted for the majority of patients.

We'll now transition over to the safety information. In an effort to capture potential events reported from the 2005 - 2006 safety related activities the FAERS search covered the period from the 2006 review through February 2016. There were 46 serious pediatric reports, including 43 deaths.

We have up on the screen now the flowchart which explains how we adjudicated the cases for discussion in today's presentation. So you see that 46 reports were received, 28 of the reports were reviewed and excluded for the reasons listed on the bottom left, and this results in a pediatric case series of 18 reports which included 15 reports of death.

We have a table up here which shows some of the characteristics in the case series. We can see that there was two cases reported in patients over 2 years of age, and

cases were reported in patients who were less than 2 years of age. In the bottom row we

can see that 14 out of the 15 reports -- I'm sorry, 14 of the reports refer to presence of pseudoephedrine.

So the summary of the safety review is that there were no new deaths that were not already accounted for in the 2006 safety review. So all the current cases in the current review were reported to FDA from 2007 earlier. All children were less than -- of the pediatric death cases, all children were less than 1 year of age. However, one case did not report an age, but stated that the patient was a baby.

Pseudoephedrine was seen in 14 out of these 15 cases. In the instance the report of the patient who died where pseudoephedrine was not listed, this was a 3 month old infant who received three doses of Karbinal ER over approximately 15 hours. Caregiver came in, noted that the patient was in distress and not breathing, resuscitation failed, and no other additional information is available.

Slide 17 presents the non-fatal serious

events. We have one case of topic epidermal necrolysis arising from or with Stevens-Johnsons Syndrome, and the patient also had leukopenia.

Please note that the patient was also treated with acetaminophen which has been linked to TEN and is actually in more recent labels for acetaminophen. There was one patient who had an undocumented seizure, and there was no additional clinical information available. The final patient was a 6 year old who experienced nosebleeds. While nosebleeds are not labeled, anticholinergics effects which can cause drying of the nasal mucous is labeled.

So that concludes the presentation. We concluded that there are no newly occurring deaths since the safety related regulatory activities of 2005 and '06. There were no new safety signals identified. FDA recommends continued, ongoing, safety monitoring. Does the committee agree? I'd like to acknowledge and thank the folks listed on this slide?

DR. HUDAK: Thank you, Dr. Hausman. Any

comments? Questions? Observations? Thank you for emphasizing the importance of accurate dosage.

All right. Hearing none we will vote on the FDA recommendation to continue their current safety monitoring by pressing buttons.

Okay. We will register oral votes. We'll start with Dr. Fischer again.

DR. FISCHER: Gwen Fisher. I concur.

DR. MOON: Mark Moon. I concur.

DR. SAVEJ: Wael Savej. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. TURER: Christy Turer. I concur.

DR. SHWAYDER: Shwayder. Concur.

DR. CNAAN: Avital Cnann. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. I agree.

DR. WADE: Kelly Wade. I concur.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: Okay. So in summary, we have unanimous concurrence with the FDA recommendation.

All right. So that brings us to the conclusion of the drugs for the day. We have five devices. We are scheduled for a break. Our dilemma is, maybe you can help me here, who's here. We have finished a half an hour before our new secret schedule. So either we can, if the people are here and we can get people here, move up the device presentations.

But our dilemma is that some of the folks show up at the time that the schedule said, so, Skip, you have any?

DR. NELSON: We think we're here. We think they're here, but we'll confirm. I know Vasum is, but whether the presenters are all here or not at this point.

DR. HUDAK: Okay. Why don't we do this?

DR. NELSON: Take a break and we'll sort

it out?

DR. HUDAK: Take a 15 minute break and plan on regrouping at 2:15.

DR. NELSON: Get all the ducks in a row.

DR. HUDAK: If people are here we'll start.

DR. NELSON: Right. Okay.

(Recess)

DR. HUDAK: We are ready to start. Let me figure out who is here. I see some new faces down at the end of the table for the Berlin Heart. Yes? So if you can introduce yourselves and then we can have Dr. Ward start.

MS. BAUER: Kelly Bauer. I'm a nurse consultant in the Office of Surveillance and Biometrics, FDA.

DR. LASCHINGER: John Laschinger. I'm a medical officer and a cardiac surgeon, Office of Cardiovascular Devices, FDA.

DR. HUDAK: One recusal on this case, Dr. Fischer. You need to push -- excellent, okay. All right. We're ready.

MS. WARD: Good afternoon. My name is Rebecca Ward. I am an epidemiologist for the Office of Surveillance and Biometrics within the center for devices and radiological health at the FDA. I will present a summary of the post-market review for the Berlin Heart EXCOR Pediatric Ventricular Assist Device or PVAD to include medical device reports or MDRs, the post-approval study results, and the literature review.

The Berlin Heart EXCOR device received HDE approval on December 16, 2011. The EXCOR in intended to provide mechanical support for the failure of one or both ventricles as a bridge to cardiac transplantation. The EXCOR consists of an extra (inaudible) and pneumatically driven blood bump and cannula which connect the blood pump to the atrium or ventricle and to the great arteries.

The IKUS provides alternating air pressure to the blood pumps through driving tubes. It can be used to support one or both ventricles. A typical biventricular pump configuration is shown in the top right of the diagram.

The blood pump is divided into an air chamber and a blood chamber by a multilayer of flexible polyurethane membrane. The alternating air pressure provided by the IKUS moves the membrane. Thus, filling and emptying the blood pump. Both the blood chamber and the polyurethane connectors are transparent to allow for the visual detection of deposits and for monitoring the filling and emptying of the blood pump.

There were 279 devices sold in the U.S. from November 30, 2014 to November 20, 2015. Fifty five patients were implanted with one or more IKUS blood pumps in the U.S. in the same timeframe. All implants were in pediatric patients.

Next, I will discuss the MDR review. The FDA searched the MDR database for all MDRs associated with Berlin Heart EXCOR from June 1, 2015, the cutoff date from the previous year's summary, through May 31, 2016. The query resulted in the identification of 32 MDRs. Here is an overview of the data for reporting country,

patient gender, and patient age as identified in the MDRs.

There were 31 pediatric patients ranging in age from 1 month to 15 years with an average age of 3.4 years. Additionally, there was one adult MDR. This slide identifies the event type of the 32 MDRs. There were zero deaths, six serious injuries, and 26 malfunctions. The shaded column highlights the 31 pediatric patients.

This chart depicts the primary reported problem in the 32 MDRs. The pediatric patients are identified in blue and the one adult patient is identified in red. The most commonly reported problem is related to defects with the pump membrane in 18 MDRs. In (inaudible) or hemorrhagic CDAs and driving tube leaks were the next two most frequently reported problems with three MDRs reported for each.

This table further characterizes the primary reported problem by event type and time to event occurred which is represented in months. Blood pump membrane defects results in three

injuries and 15 malfunctions occurred between 1 and 8.9 months. As indicated in the executive summary, the firm incrementally implemented a number of changes from 2013 to 2015 to mitigate membrane layer defects.

Pumps manufactured after June 2015 include all of the changes. Only one of the 18 reports of membrane defects involves a pump manufactured after all of the changes were implemented. This device problem will continue to be monitored over the coming year.

There were three injury CVA events which occurred between 0.3 and 1.7 months. Additionally, there were two events in the same patient involving arterial outflow cannula leaks which occurred at 1.7 and 2.8 months. Microscopic analysis of the first case identified a small cut or incision on the outer service of the tubing, allowing a drop of blood to leak through. The second device was discarded and not evaluated.

Based on the investigation of both events, it was determined that the 1 year old

patient was chewing on the cannula connecting set and likely caused the leak. According to the IFU and physician's manual, clinicians are instructed on the appropriate cannula length, proper maintenance and assessment of the cannulas and blood pump, and avoiding kinking or bending of the cannulas.

The IFU was updated in 2015 to include stronger precautions on cannula care and activity restrictions. This added statement included the potential for injury or death if cannula damage occurs. The FDA is continuing to monitor this issue. All of the events reported in the MDRs are further described in the executive summary.

The table compares the reported problems from this year's analysis to the number of MDRs from the 2015 PAC analysis. Note, that this table is not an exhaustive list and therefore, does not include all reported problems from last year's analysis. And the totals will not equal 100 percent. As you can see, the top reported problems are consistent with last year's analysis.

To summarize key points, the injury and malfunction MDRs related to CVA, membrane defects and driving tube leaks are similar to reported events from the previous year and in the IDE. The firm has made design and manufacturing changes to mitigate membrane defects and driving tube leaks.

FDA will monitor for additional events over the coming year. The IFU was updated in late 2015 with stronger language regarding care of the cannula and patient activity restrictions. There are no other safety concerns at this time.

I will now present an update of the post-approval study and the systematic literature review. Upon approval of the EXCOR HDE in 2011 FDA required one post-approval study as a condition of approval. The post-approval study is an all comers perspective registry of patients implanted with the EXCOR device. The primary purpose of the study was to evaluate the safety of this device by demonstrating that the series adverse event rate or SAE rate is not greater than the rate observed in the IDE study.

Enrollment and obtainment of the primary endpoint of interest was complete prior to last year's PAC meeting, and clinical outcomes for all 39 subjects were reported. That's the light grey shaded box on the top left.

The safety endpoint was also met. The SAE rate in the post-approval study was lower than the SAE rate overserved in the IDE study by a statistically significant margin. The post-approval study continued after the obtainment of the primary endpoint of interest. All 27 subjects that survived to successful heart transplant or weening were eligible for continued follow up for an additional 24 months.

The purpose of continued follow up of the surviving study subjects is to assess lower term functional outcomes and quality of life that may be associated with use of the EXCOR device. In addition, FDA thought to obtain more information regarding the evolution of neurologic outcomes for patients surviving stroke that occurred while on EXCOR support.

Twenty five subjects have contributed continued follow up data and 20 of those have completed their 24 month post-EXCOR or post-transplant visit. Additionally, late neurologic and clinical outcomes for the five subjects who survived following a strike while on EXCOR were assessed.

The most complete functional outcome assessment was collected using the FS-II. The FS-II assesses general health and life stage specific factors for the child over a two week period. Children ages 0 months to 11 years can be evaluated. The questionnaire is completed by the primary caretaker, and scoring is calculated as the percentage of the maximum number of points for a specific age range with higher scores being better.

This assessment was completed for the majority of study subjects at baseline and 12 months post-EXCOR or transplant. As shown in the grey, highlighted column, total scores, general health scores, and responsiveness, activity,

interpersonal functioning scores showed statistically significant improvement from baseline to 12 months post-EXCOR or transplant. The 24 month results are provided in your executive summary and showed similar score improvement from baseline.

The pediatric stroke outcome measure of PSOM is used to assess outcomes after strokes in pediatric patients. Specifically, PSOM scores deficits for five domains, summarized on this slide. Each of these five domains can be scored from 0 to 2 with 0 indicating no deficit, and the score of 2 indicating severe deficit. A total maximum or worse possible score across all five domains is a score of 10.

Scores may change over time with progression, a regression or neurologic deficits. And a total score of 2 or greater is indicative of a severe deficit.

Five subjects that experienced the stroke while on EXCOR support survived, two, a successful transplant or a weening. The patients'

clinical neurological status allowed for performance of a transplant in 80 percent of those affected and surviving. In three of the five, regression of the severity of the neurologic deficit was observed.

The firm also provided brief clinical notes on the current health status of these subjects, shown on the grey, highlighted column on the right. Based on these clinical summaries, four of the five subjects are doing well or showing some improvement.

Summarizing the PAS update. Survival after transplant or successful weening is high. Subjects that survive to a transplant after a stroke are reportedly improving or doing well. While limited data are available regarding the longer term quality of life and functional outcomes for study subjects, the assessment with the most complete data shows statistically significant improvement in functional outcomes from baseline to 12 months post- transplant or EXCOR.

No additional concerns are raised from the longer term follow up of subjects then this post-approval study. A literature review was also conducted to update the probable benefits and risks of the device. In June 2016, a search off the PUMA database for articles published since last year's search was performed using the same search terms and limits as last year.

These search terms and limits are included in the executive summary. The inclusion/exclusion criteria on flow chart for the literature reviewed are displayed here. Of 15 potentially relevant articles, five fit the criteria for qualitative synthesis. Five retrospective cohort studies were identified, and the majority of these cohorts were European.

One study included both pediatric and young adult populations. The four other studies were pediatric only populations. The median age of patients in these studies with pediatric only populations range from 23.8 months to 9.1 years. Patients included in these retrospective studies

were implanted with an EXCOR device as early as 1990 and as last as 2014.

Survival while on EXCOR ranged from 65 to 90 percent and survival to transplant ranged from 61 to 81 percent. Time on device and time to transplant varied by patient. Average time on EXCOR device, and average time from EXCOR to transplant was not consistently reported in these studies.

Two studies were designed to evaluate survival in subpopulations that may have more inherent risk. In both of those studies the patient sub-groups with potentially more inherent risk, single ventricle patients on one study, and patients needing multiple, mechanical, circulatory support modalities in the other study had similar survival compared to their study counterparts. The commonly report complications in the literature are neurologic adverse events including hemorrhagic CVA and thromboembolic events, as well as thrombosis and infection.

Neurologic adverse events were

heterogeneously reported across studies. The proportion of subjects experiencing hemorrhagic CV and thromboembolic neurological adverse events was highest in (inaudible) 2016. That study had data on patients implants with an EXCOR device as early as 1990. The authors noted that post-implantation anticoagulation therapy was modified in the year 2000. However, the authors did not break down stroke rates by time period.

Device related infection was also reported in two studies, and the proportion of subjects with these events varied greatly. The highest proportion of subjects with device related infections was also reported in (inaudible). The authors noted that 67 percent of patients had skin infections around the EXCOR cannula.

To summarize the literature reviewed this year, EXCOR continued to be associated with a relatively high rate of survival while on device and survival to transplant. Use of EXCOR also continued to be associated with neurologic adverse events and infection. However, the adverse events

observed in this year's literature search are similar across what was observed in last year's literature search, the IDE study, and the post-approval study.

In summary, FDA's review team has identified no new safety concerns since the 2015 PAC meeting, and concludes that the probable benefit/risk profile of the device for the pediatric population continues to support the HTE for which the exemption was granted. FDA will continue surveillance and report updates of the following to the PAC in 2017: the MDR review, the mandated post-approval study review, and the literature review.

FDA would like to ask the committee, does the committee agree with FDA's conclusions and proposed approach? Thank you.

DR. HUDAK: Thank you. So this is, for members on the committee who have been here the past few years, this comes up annually, so this is a new annual update and open for discussion.

It's nice to see that the membrane issue

has been addressed. But, I guess, maybe the reporting is lagging behind as some of the old units are being deployed. So, Dr. White?

DR. WHITE: Just quickly, how many of the older units remain in inventory that can be used going forward? Do we have that information or did they replace all the units in inventory across the spectrum?

MS. BAUER: There are still older units out.

DR. WHITE: Do we have any idea why? How many and why, actually?

DR. KEPPLER: (inaudible).

DR. WHITE: Pardon? I'm sorry. We can't --

DR. KEPPLER: Sorry. The sponsor will get back to us about that.

UNIDENTIFIED MALE: Is it possible to just change out the membrane in the device? No.

DR. WHITE: Is there a reason not to replace the units in inventory, other than costs, if they're a safer device?

MS. BAUER: I do know that it does take quite a bit of time to manufacture one pump. I think it's over a month, as well, so I think that's cost and the availability. Cost and availability, but they are working on more pumps.

DR. WHITE: Thank you.

DR. HUDAK: Okay. Dr. Havens and then Dr. Hoehn.

DR. HAVENS: Peter Havens. I just had a data clarification issue. Table 1 in the backgrounder suggests that there was no change from the 2015 analysis to the 2016 analysis in the membrane defect data, but you said, starting in July 2015 we're down to one. I just didn't understand. At least that's what I understood you to say. So I'm just trying to understand what the answer is.

Then, if there's really only one since 2015 what's the denominator? So Table 1 has an MVR count, in the 2015 analysis of 22 in that 2016 analysis of 18 -- this is just for the membrane defect. But then the statement was that since the

change a year ago there's been one membrane defect, and I'm not clear why the numbers don't add up? Then one out of how many implanted is the question.

DR. LASCHINGER: Yes. I think what it meant is that there's only -- of the membrane defects that are listed on that table only one came from a device that was manufactured with all the changes. As you just heard --

DR. HAVENS: Got it, okay.

DR. LASCHINGER: -- all the changes -- all the devices with changes have not yet been distributed throughout the whole system and there's still old devices in the system.

DR. HAVENS: I understand. So in Table 1 there are old devices that have the old membranes.

DR. LASCHINGER: Mm-hmm.

DR. HAVENS: In the new membranes, how many new -- therefore, the question is, how many devices with the newer membranes serve the analysis with one in the numerator.

DR. LASCHINGER: I don't know the answer to that question as far as how many of the new devices have been implanted as of yet, in the U.S. market.

DR. KEPPLER: In this dataset that she's showing we didn't do that analysis. I hear you asking what the denominator was for devices that had all the changes compared to the one that had an issue and we didn't prepare that together with FDA for this meeting.

DR. HAVENS: Thank you.

DR. KEPPLER: If I heard you right.

DR. HAVENS: Yes, no. That's the question. It sounds like the membrane was identified as a problem. The defects in the membrane have been changed. In the changed membranes there's only been one reported problem associated with the membrane. But then the question is how many of the new membranes have been used that serve as the denominator for that estimate of one in the numerator.

Yes, ma'am?

DR. KEPPLER: Yes. I understand your question.

DR. HAVENS: Well, good. Okay.

DR. KEPPLER: We'll have to look at that with you in the future.

DR. HAVENS: Okay.

MS. BAUER: Because we can't get at that in the next couple minutes.

DR. KEPPLER: NDRs don't have that denominator data.

DR. HAVENS: We'll ask for that specific number in the response.

DR. LASCHINGER: Thanks.

DR. HUDAK: Dr. Hoehn?

DR. HOEHN: My question's corollary to that. I was also confused about the 2015 membrane data. Because it looks like there were 18 cases where there was still a malfunction and then they differentiated 18 that malfunction and three injury, so I wanted some clarify. What was the injury to the patient? Because I think there's a difference when the device malfunctions and it has

to be switched out to a new one or the membrane has to be changed versus what the impact is with the patient?

So I didn't know if you could elaborate on the differences between the three injuries that occurred from out of the 18 membrane issues. Because it certainly sounds like there's still old membranes in use. Does that question make sense?

DR. LASCHINGER: Injuries are things that result in either hypertension, tamponade type physiology for the pump. So when you get the membrane defect, basically, it's a space occupying legion occurs due to, depending which layer ruptures, due to air or blood inside the device. So in some of them you get the need for another procedure to change the pump out, where the patient becomes briefly hypotensive.

Two of those three that was done without difficulty or effect on the patient. The third patient had a low cardiac output, and they also had the pump exchanged and at some point later, due to poor status overall, it was decided to

remove support. But it wasn't directly as a result of that incident. That incident certainly didn't help things along as far as taking care of the patient, but the demise of the patient wasn't directly a result of that event. So those are the three injuries.

DR. HOEHN: So just to --

DR. LASCHINGER: It's in the summary, so you can actually read them, but those are the three injuries.

DR. HOEHN: Okay. But if there's a membrane problem you don't switch out the membrane? You can't just - -

DR. LASCHINGER: No. You switch out the whole pump.

DR. HOEHN: -- switch out one membrane. You switch out the whole pump?

DR. LASCHINGER: Yes.

DR. HOEHN: Okay.

DR. LASCHINGER: In the same way --

DR. HOEHN: I was just trying to clarify.

DR. LASCHINGER: The same with pump thrombosis, when you see a thrombus in the pump. It's a clear pump, so you can see it and thrombus tends to occur in some patients, especially near the inflow and outflow valves. When you see that you can change out the pump electively.

The membrane rupture occurs a little bit more suddenly and has more hemodynamic effects, depending on how much pressure there is on the sac as far as allowing it to expand fully. So that kind of occur more acutely.

DR. HOEHN: Okay. But the injury was more from the fact that the pump's not working there. So it's everything related to health failure from their underlying condition?

DR. LASCHINGER: Yes, yes.

DR. HOEHN: And then the emergent process to change out the pump?

DR. LASCHINGER: Yes.

DR. HOEHN: Okay. Thank you. I just wanted to be sure I understood.

DR. LASCHINGER: Mm-hmm.

DR. HUDAK: I will take Dr. Shwayder and then Dr. Cunningham. But could the speaker from the audience stand up again and introduce yourself and your name for the record?

DR. KEPPLER: I'm Mary Beth Keppler from Berlin Heart.

DR. HUDAK: Okay. Thank you. Okay, Dr. Shwayder?

DR. SHWAYDER: So I'm looking at Table 3 in the Berlin 2015 update. Because I was curious how long these are left in because they're a bridge to transplant, and I noticed that most are, like, 0 to 79 days, but there are a few outliers.

I'm curious if the system failures of the pump are related to age that they are operating? Does that make sense? If you have that data because it doesn't show up in the other tables.

DR. LASCHINGER: I'm looking to see one thing.

DR. SHWAYDER: In other words, is there, like, four months out we should think about

switching these things out?

DR. LASCHINGER: No. There's been nothing that we've seen as far as the time period that would recommend changing out the device. The devices are examined several times a day as matter of routine to look for thrombus and to look for problems like this. But there's not been a specific time period where a recommendation's been made to change out the device because it increases the chance of membrane rupture. No.

DR. HUDAK: Dr. Cunningham?

DR. CUNNINGHAM: Sure. One other question related to the three injuries. Are any of the three injuries or several of them with patients who got the device with the new changes?

DR. LASCHINGER: Not that I'm aware of, no.

DR. HUDAK: Dr. Campbell?

DR. CAMPBELL: So it looked like in the original patients there was a 33 percent stroke risk. Is there

any way to -- is there any surveillance

to understand whether or not that risk is rising or falling since that's one of the clear safety risk?

DR. LASCHINGER: Yes. It was --

DR. CAMPBELL: It's one of the clear safety risks.

DR. LASCHINGER: It was 30 percent in the PMA. I'm sorry, the HDE application, I'm sorry. It's been about

percent consistently in the literature throughout. The one study, actually most of these children have been anticoagulated using what's called the Edmonton Protocol that uses both anticoagulant and two antiplatelet agents.

There is some promising work being done out of Stanford, but it's only been published so far in abstract form. But I can tell you that with that they've been able to affect an 80 percent reduction in both stroke rate and bleeding complications using a revised anticoagulation protocol. That's only at one center so far. Whether that pans out when it's expanded to more

centers or is due to something about the local care of those patients we won't know until they do it.

But, certainly, I think there's some work to be done on the anticoagulation protocol with these devices to make it more effective. Both from preventing thrombolytic complications and bleeding complications, both.

DR. CAMPBELL: Is the new protocol, is that a higher dose of anticoagulation --

DR. LASCHINGER: Yes.

DR. CAMPBELL: -- or a lower dose.

DR. LASCHINGER: A higher dose of antiplatelet agents, same dose of anticoagulants, but a higher fixed dose of antiplatelet agents that are not based on, you know, bench testing of their effectiveness, but rather on fixed higher doses.

DR. MOON: Are we assuming that all the intracranial bleeds then were from an embolism, and then became an intracranial bleed?

DR. LASCHINGER: No. That's not true.

Some were intracranial.

DR. MOON: Spontaneous?

DR. LASCHINGER: Yes.

DR. HUDAK: Dr. Havens?

DR. HAVENS: Is it possible to address the issue about taking the old membrane devices off the market and replacing them all with new membrane devices or is that not a possible part of the discussion?

DR. HUDAK: I think someone from FDA can discuss that.

DR. NELSON: I would let Dr. Pierce, perhaps address, whether that's doable in the threshold for

(inaudible) to be able to do that. But since there's some new folks around the table let me just give you a quick framework about the device reviews.

If you look at MDRs, so it's basically 2007 the committee receives these reports of these adverse events and basically then we obtain any

recommendation as to whether there should be any action taken in response to those adverse events. And so that's what it specifically says, including obtaining any recommendations of such committee which gives you all about actions to take. So that's the language, in a very general way.

So if you think you all want to make a recommendation, I don't know if that's actually doable and what the threshold is for doing that. Folks from CDRH, perhaps, could address that.

DR. LASCHINGER: The removal of the devices though from general use for this purpose without the ability to place them all and all the size ranges would result in a shortage of the devices and an inability to use them. So although that would be the ideal solution, without the ability to replace the devices easily and simultaneously it would result in some shortages that would be detrimental to overall patient care.

DR. HUDAK: So I would suggest that we do not have data yet on the whether or not the rate of membrane defects per membrane month has

changed. So I think making any sort of a recommendation without those data would be premature.

DR. MOON: Does the redo have to -- is this a redo sternotomy? To put the new device -- you can just change it out in the pocket?

DR. LASCHINGER: It's on the outside. It's external.

DR. MOON: So that negative of having to change out a bad membrane is really not that big of a deal?

DR. LASCHINGER: No. And it's the same process that's done for changing out a device when there's thrombus in the pump as well. So it's a device that every center knows how to do. That every center can do well.

The only difference would be in if there was an acute hypomanic event with the membrane rupture that caused a hemodynamic problem. The devices are three layers on purpose so that you don't -- there's never been an event where you got air in the systemic circulation because of a three

membrane rupture which is what it would take.

So really what it does cause is just space between the membranes to enlarge, causing a tamponade like effect either from air or from blood, depending which membrane ruptures.

DR. MOON: And that doesn't create potential for clotting and stroke?

DR. LASCHINGER: No. No, it just basically decreased the forward output of the pump.

DR. MOON: So I would suggest that that negative wouldn't rationalize creating a deficiency in devices.

DR. LASCHINGER: Yeah. No, yeah, yeah. Right.

DR. MOON: I think that negative shouldn't force us to pull every device off so that we don't have enough of.

DR. LASCHINGER: Yes, I would agree.

DR. HAUSMAN: Just to add to this discussion, I think to reiterate what Dr. Laschinger mentioned. It would be a significant

public health and deficiency and deficit to actually pull these devices off and not have them available for use when necessary. Especially considering the relatively low rate of the membrane ruptures. Just want to clarify that.

It would also be for us to consider a recall issue, and that would also be a very different process.

DR. HUDAK: Dr. White?

DR. WHITE: Michael White. Is it fair to say that the performance of the device has not changed significantly since we approved it, and this is simply an improvement to lower the risk of the device? So we're not really saying the device is more dangerous than we expected when we put it on the market?

DR. LASCHINGER: Yes.

DR. WHITE: We're just looking for ways to improve the outcomes. Is that a fair assessment?

DR. LASCHINGER: Yes. I think that's true. I think we knew about all these problems

when we approved it. The problem was is, obviously, when there's no other device to treat children in this age range at this point in time. So with all the warts and all, I guess, I don't know what I -- you know, we approved this knowing that, obviously, things could be improved.

I think the company has been very forthright in trying to improve the defects we saw with the mechanics of the device, things like membranes and things. And I think other researchers are very aware and very concerned about the risk of stroke and things like that, and are working actively on different anticoagulation regimes that would address that.

There has been a study of the patients in the IDE study looking at their anticoagulation regimes, their various lab measurements along the way to see if there were any predictors of stroke that could be identified in advance to tell people when they would need to either be aware that a clot might be close to forming or be at risk of forming, and nothing has been identified that

would allow that prediction.

So I think changes in the anticoagulation regime which are being looked at now are probably the most efficient and promising way to go.

DR. HUDAK: Two more questions. Dr. Cunningham and then Dr. Hoehn.

DR. CUNNINGHAM: So we're stating that this is an improved device. I would say it's a new device, but since we have no idea of the denominator I don't think we can say it's an improved device. I don't know what our recommendation would be in terms of how soon you would come with that data of the denominator so we could make some real judgement.

DR. HOEHN: Sorry. One last technical question just to be sure I understand. So when the membrane ruptures you change the pump, but all the cannulas stay the same?

DR. LASCHINGER: Yes.

DR. HOEHN: Okay. Thank you.

DR. LASCHINGER: Yes. And the pump is

totally on the outside of the body.

DR. HUDAK: Dr. Nelson?

DR. NELSON: Just a point of clarification. A humanitarian use device is an approved device. It's under the humanitarian use device exemption, so from that standpoint the evaluation of safety, I think is, you know, knowing the denominator is a separate question. So I'm not sure what you mean by approve the device.

DR. CUNNINGHAM: I think I didn't speak clearly enough. I said improved, not approved. So we're saying it's an improved device, but I don't think we can state that until we know the denominator.

DR. NELSON: Thank you for the clarification

DR. LASCHINGER: Yes. We agree. You know, we approved the changes in the device based on bench testing and those things that might predict better longevity for the device and the membranes. But until we have the clinical

evidence we don't know either, and it's too early in its use to make statements about whether or not it's improved or not. So I think you're right.

DR. HUDAK: Dr. Moon, will you have the last word?

DR. MOON: Yes, I've got one last question that might take all afternoon to answer. In your review of the literature you had stroke rates of 3 percent in one study and 47 percent in the other study. That just doesn't make any sense to me. Do you have an explanation for that? Is somebody not reporting them? Because we really can't make any conclusions based on that.

MS. BAUER: I completely agree. (inaudible) study with the higher rates were both infection and stroke had patients enrolled as early as 1990 and followed our HUD patients enrolled as late as 2014. The Sandica study, if I'm remembering correctly, their earliest subject was implanted in 2008, and their latest subject was implanted in 2014.

So I would assume that there would be

differences in both the device and the, as the author noted, the anticoagulation therapy over time. It's possible that the stroke rates were higher earlier in the (inaudible) study, and that may attribute to the higher rate observer here. But, I agree that they're vastly different and it's very hard to make any kind of conclusion from that.

UNIDENTIFIED MALE: I'm just going to add to that, just to clarify, because you brought up a very poignant issue when you asked the question about the change in the anticoagulation regime. The anticoagulation regimes are revolving with respect to use of the device.

You also pointed out whether all these strokes that we experienced in these patients are related to a thromboembolic event versus a spontaneous, quote/unquote, occurrence. Because, certainly, spontaneous occurrences can be exacerbated by increased or overdone anticoagulation. So, again, all of these issues are evolving in terms of managing the pump and the

patient at the same time.

DR. LASCHINGER: I think the rates that we're seeing in studies that we've done are probably the most accurate due to the way that they were all, you know, assessed and adjudicated. The other studies are doctor reported strokes, and they're not assessed or adjudicated the same way.

The Heser Study, in particular, involved both adults and children and stretched over a period of almost 25 years. So, you know, but overall, I think you can say there probably is about a 30 percent stroke rate, as we've seen,

to 33 percent. That one third of those are probably hemorrhagic. The other two-thirds are thromboembolic, and that stroke does contribute to death. We know that. But if the patients survive their stoke most of them actually go on to transplant.

Once the patients do end up going on a transplant, which about two-thirds do, survival is the same as any other transplant patient long term, so. In general, those are the conclusions

you get from reading the entire literature.

DR. HUDAK: Dr. White, last question.

DR. WHITE: Your reporting was so great on percent. That percentage is not key to time on pump. It's not keyed to any other indication. It's just the percentage of patients that had that complication.

MS. BAUER: Yes.

DR. WHITE: Unless we have some other means of assessing the stroke, 3 percent may have been because the kids were transplanted very rapidly. I don't have that study to look at to see if those rates mean anything.

MS. WARD: Time to transplant and time on device varied by study. I don't remember a large variation between the time on device and time to transplant between the studies. I have the numbers over there. I can get them for you.

I agree, it would be much better to have rates, but this was what was provided in the literature.

DR. WHITE: Thank you.

DR. LASCHINGER: Yes. And in the IDE study they did report the adverse events in terms of events per days of patient support. So those have all been reported and they're publicly available.

We do require the sponsor to report events as events per patient day of support.

DR. WHITE: When we look at the literature, if we could put that number in when you bring this back next year, because I know you will.

MR. LASCHINGER: Okay.

DR. WHITE: It would be helpful to us for our deliberations if we had an event rate per days, patient days or something like that to help us make this determination. Thank you.

DR. HUDAK: So let me just summarize. I think really what a couple of the committee members are asking for are more sophisticated analysis of event versus time which you don't really get at by events per patient day. So that requires some statistical tour de force analysis

on existing data, but I think that would be useful to look at.

If you can bring up the slide, the last slide, the summary slide, so we can get to the recommendation. So with your buttons, we'd like to vote on the question here, the recommendation that the FDA will present to us in 2017 the results of their next review which includes new patients and literature findings, and maybe I can also add into that a little bit more information on, sort of, this time event analysis. Also, a better discrimination of the events on the old membrane pump versus the new membrane pump.

Okay. So we'll go around the room. I think. Dr. Anne, you're up. Come around this way.

DR. ANNE: Premchand Anne. I concur.

DR. WADE: Kelly Wade. I concur.

DR. WHITE: Michael White. I concur. And I would ask that you try to stratify the data that you present to us for events based on the size of the device, and some discriminator of how

time to events -- I'm not sure of the best way to do that, but help us come up with a better descriptor.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. CNAAN: Avital Cnaan. I concur. I would also suggest looking at the subject year exposure when you compare old to new.

DR. SHWAYDER: Shwayder. Concur.

DR. TURER: Christy Turer. I concur.

DR. HAVENS: Peter Havens. I concur.

DR. SAVEJ: Wael Savej. I concur.

DR. MOON: Mark Moon. I concur.

DR. HUDAK: Okay.

DR. LASCHINGER: Can I just make one?

DR. HUDAK: Yes.

DR. LASCHINGER: For pure MDR reporting

we don't have a -- I just want to make sure the committee understands that we do not have a denominator, so we can't tell you what the rate is based on the entire U.S. experience. We can only tell you what MDRs we have, and in Table 2 in your summary, the time to event for each of those MDRs is noted.

So for those noted MDRs we can give you a time to event. But how that compares to patients, it doesn't take into account the patients who didn't have those MDRs, and so it's going to be a very -- it's not going to be representative of patients overall, but only for the patients who had that MDR.

If we can get that data to you. Just so you know.

DR. HUDAK: Sure. But can I ask a naïve question then?

DR. LASCHINGER: Sure.

DR. HUDAK: So there are relatively few of these devices actually in use.

DR. LASCHINGER: Mm-hmm.

DR. HUDAK: Are you reporting on a complication rate of 33 percent of strokes, so there aren't that many devices that are out there in use for which complications have not been reported. So it seems to be a relatively simple matter of working with the company, perhaps, and finding out which patients for how long have been on these pumps and factoring that information, which is all negative data. It's just going to -- I mean, pretty straightforward it seems to be. But I guess the consensus is to do the best you can with what you've got.

DR. LASCHINGER: No, I understand. We intend to do that.

DR. HUDAK: Yes, right.

DR. LASCHINGER: I just wanted to point out the shortcomings of the reporting systems that we have available to us.

DR. HUDAK: Okay. Good.

DR. LASCHINGER: I don't want to have unrealistic expectations.

DR. HUDAK: All right. We'll do a

question after the vote.

DR. HOEHN: It was another clarifying question about what you said because I guess I incorrectly assume that because it was a humanitarian exemption of an IND that every time a Berlin Heart was used it was reported to the FDA. So you're saying that's not true? Only the adverse events are reported to the FDA? And there's not some database somewhere similar to (inaudible) where use is tracked?

There's no one person out there other than the company who could tell you how many times a Berlin Heart's been used in the last 365 days?

DR. LASCHINGER: We can get some of that information through annual reports and things like that, yes. But, yes, we can get a lot of that information that way, so.

DR. HUDAK: Okay. Well, thank you very much. We will move on to the next topic which is CONTEGRA, pulmonary valve conduit. Are we changing anybody out at the table? Yes, we're changing out. Okay.

So if you could introduce yourselves?

MS. CHIH-HSIN LIU: This is Jenny Chih-Hsin LIU. Nurse consultant in CDRH and Biometrics.

DR. KURTZMAN: Dr. Steven Kurtzman. I'm a cardiologist in the division of cardiovascular devices in the center for devices.

DR. HUDAK: Okay. Dr. Aggrey, you're on.

DR. AGGREY: Good afternoon. My name is George Aggrey. I'm an epidemiologist at the Office of Surveillance and Biometrics, CDRH. I will present CDRH and our review for the CONTEGRA HDE, including a review of the medical device reports and the published literature since our last PAC briefing in 2015.

The CONTEGRA pulmonary valve conduit was approved in November 2003 with indications shown on the slide. The HDE annuaal distribution number for the CONTEGRA device is 4,000. Since the last PAC review one year ago, a total of 428 have been implanted with the majority in the pediatric

population.

Next I will present information related to the medical device reports received by the FDA. Since the last PAC review, as noted in our executive summary, a total of 79 MDRs related to the CONTEGRA device have been received by FDA in the one year period since our last update.

However, the number of unique reports after removing events tied to published literature which was covered at previous PAC meetings, which will be discussed in our literature review in a couple of minutes, is 58. Fifty three of those 58 MDRs provided information about a patient's age, and of those 48 were for pediatric subjects. The mean age in these reports was approximately 9 years.

This slide, which also appears in your executive summary breaks out the 48 pediatric reports by primary event type. As seen on the slide, stenosis was the most commonly reported adverse event and accounted for 50 percent of the pediatric events. Of note, all of these cases

required device replacement or conduit and angioplasty. An additional

MDRs reported device placement, but did not specifically mentioned stenosis as the reason.

Three of those cases were situations where the patient outgrew their device, and the remaining MDRs provided no specific reason for the replacement. As can be seen on the two right-hand columns. The mean time to stenosis or device replacement for the (inaudible) set of MDRs was approximately 75 months. Stenosis and device replacement reflect anticipated long-term events given the young age of the majority of the pediatric patients at the time of CONTEGRA implants.

When comparing MDRs for this year's PAC report to that presented in 2015, the types of events reported, regardless of patient age, are similar. Although, as would be expected with the passive reporting system, the absolute numbers and percentages varied. In summary, the MDRs received since the last PAC meeting identified no new types

of safety issues.

I will now present the results of FDA's literature review. A search of the (inaudible) and databases were conducted using the same search terms as last year's search and is discussed in your executive summary. This slide shows the article selection process which resulted in a total of 11 articles for final review. These 11 publications are discussed in detail in your executive summary, and I'll only be highlighting some of the more relevant points in the next few slides.

Three of the studies and all case reports included only pediatric patients. In the next two slides I'll present data from the two publications which contain more than one CONTEGRA recipient. Sarikouch et al published a recent retrospective study which compared outcomes of patients who received CONTEGRA and sterilized pulmonary homographs or (inaudible) homographs.

Each group consisted of 93 patients, and the mean follow up ranged from 5 to 7 years for

the three cohorts. The highlighted numbers represent outcomes (inaudible) a significant difference between CONTEGRA and the sterilized pulmonary homograph or (inaudible) homographs. (inaudible) from implantation and peak pressure gradient of 50 meters or more was (inaudible) for CONTEGRA.

However, the failure for insufficiency and endocarditis were comparable in all three conduit types. As studies by Kido et al and routine pediatric patients who have received small caliber CONTEGRA device. The patient population included young patients with low body weight and patients who have persistent pulmonary hypertension with post-operative pressure gradient about 60 millimeters of mercury.

Through 10 months of follow up, the mortality rate was 15.4 percent, and the rate of freedom from re-operation was approximately 54 percent. The office concluded that low body weight at operation and persistent pulmonary hypertension may have contributed to early graph

failure and re-operation in the study patients. As such, results contained two studies which included both pediatric and adult recipients of the CONTEGRA.

The percentage of pediatric patients aged less than 18 years in one study was 92 percent. Unfortunately, we're unable to determine the percentage of pediatric subjects aged less than 18 years in the other study.

In this first study, (inaudible) colleagues analyzed patients who underwent placement with evolved conduit, including 208 pulmonary homographs, 121 aortic homographs, 245 CONTEGRA graphs, and 137 porcelain hectographs. After a median follow up of 7 years the CONTEGRA was the only graph observed to be associated with a lower risk of reintervention and replacement when compared to pulmonary homographs.

The same study also reported rates of freedom from endocarditis of 10 years. As can be seen on the slide, fewer CONTEGRA recipients were free of endocarditis when compared to patients who

had received any of the other three conduit types. The use of CONTEGRA was observed to be associated with a nine time greater risk of endocarditis compared to homographs, as shown on the slide.

In the second study, (inaudible) evaluated 444 CONTEGRA conduit and 267 homographs implanted in patients and stratified their results by age group. This slide shows (inaudible) for freedom from explantation stratified by age group, compared by conduit type using log ran tests.

The office reported that the freedom from explantation was significantly better for CONTEGRA compared to homographs in patients younger than 1 year, the top left on the slide, and in patients 1 to 6 years, top right on the slide. In patients 25 to 40 years the results were similar.

This slide summarizes the rare adverse events that were noted in either of the studies or case reports. One case of each event was

reported, namely, coronary artery compression, thrombosis, (inaudible) section, and protrusion of the device between (inaudible) due to size mismatch. More details on these events are provided in the executive summary. These rare events, including size mismatch, are already included in the instructions for use.

The ability to draw conclusions from the literature review is limited by the following factors. Majority of the studies were retrospective. Thus, covariates were not balanced in comparing CONTEGRA to homograph or post-line heterography in at least one study. Therefore, the study result may not be as robust as for a randomized, controlled trial.

Follow up time varied in comparing CONTEGRA to other conduits which could influence the observed rates. The CONTEGRA conduit when implanted over a long timeframe, 1999 to 2014, and the standard of care may have changed during this period of time. The literature findings are not consistent across studies. In the studies with

(inaudible) patients only, the literature showed that compared to homographs, the CONTEGRA has lower rate of freedom from explantation and peak pressure gradient of 50 millimeters of mercury or more.

Comparable rates of freedom from moderate insufficiency, and comparable rate of freedom from endocarditis. In the studies with pediatric and adult population, compared to homographs or other conduit the CONTEGRA showed lower risk of reintervention and replacement. Higher rate of freedom from explantation in patients younger than 1 year and in patients 1 to 6 years, and lower rates of freedom from endocarditis.

CDRH concludes that there are no new (inaudible) regarding the safety of the device identified since the last PAC meeting. The endocarditis was consistent with the data previously reported in the literature that was presented to the PAC in the past. The ADN for this device remains appropriate for the pediatric

population for which it was granted.

FDA recommends that we continue surveillance and report similar information to the PAC in 2017. Does the committee agree with CDRH conclusion and recommendation? This ends FDA's presentation. Thank you.

DR. HUDAK: Thank you, Dr. Aggrey. So this is open for discussion. Dr. Fischer?

DR. FISCHER: I was just wondering if we have more information about the dissection that was reported in 2016? Whether there was an evaluation of the explanted device? Whether physical or structural evaluation?

DR. AGGREY: Well, regarding the literature, from what was reported in the literature we do not have any -- the information we have from the literature was that the dissection occurred about 5 millimeters approximate to the

(inaudible) stenosis. Essentially that was the information that was provided. The CONTEGRA was

explanted and replaced with a homograph.

DR. FISCHER: But there weren't any further evaluations of the explanted device looking for a structural defect that led to the dissection, as far as we know, it sounds like?

DR. AGGREY: We did not get that from the literature. Thank you.

DR. HUDAK: Dr. Moon?

DR. PEIRIS: Just as an addition to that question that was asked. Sorry, I don't think I ever introduced myself. Vasum Peiris. I'm the chief medical officer for Pediatric Special Populations at CDRH.

But in addition to the point about the dissection, it was also unclear whether there could have been potentially a surgical issue, meaning inappropriate scalpel going across the conduit area. So none of those issues were clear. So I don't want to make the point that this is specific to a fidelity, integrity problem of the conduit itself.

DR. HUDAK: Dr. Moon?

DR. MOON: Two things. One, can you go to the slide before because it's hard to answer that question without knowing what you're -- no, what your recommendations were. Yes, right.

One of those studies you said had a 10 month, 50 percent reoperation rate? That's horrible.

DR. AGGREY: Yes. That is true.

DR. MOON: That was all in very young patients or was it?

DR. AGGREY: That is true. That was in very young patients. The mean -- the median, body weight for the patients was about 5.5. The total population was 13, only

patients.

DR. MOON: That was a single center that...

DR. AGGREY: That was a single sector. And the patients also included other -- the others mentioned patients who had were very -- had a very small body weight, and they also had severe

pulmonary hypertension, and they believe that it could be attribute -- the pulmonary hypertension could have contributed to the graph failure.

DR. MOON: And the mortality rate was?

DR. AGGREY: The mortality rate was 15.4 percent. And that was --

DR. MOON: And that wasn't an operative mortality rate? That was a mortality at 10 months or...

DR. AGGREY: The mortality was two out of 13 patients.

DR. MOON: Okay.

DR. AGGREY: One patient died one month after the procedure, and the other patient died two months after the procedure.

DR. MOON: Well, it will be interesting to see what that group has as their results in the next 13 patients because that -- those are very bad. I don't know if it's grouped dependent on the surgical group that was doing the procedure or the -- it doesn't sound like it was the device because nobody else has had that bad of results.

DR. PEIRIS: Just to help clarify as well, because this might be a nuance of the pediatric cardiology subspecialty, but the younger the patient is when these devices are placed, which may already be assuming that more rapidly the conduit likely will need to be changed due to increases in body surface area and flow demands.

DR. HUDAK: Dr. Anne?

DR. ANNE: Just to follow up on the point that Dr. Moon had which was what were the causes of death for the two patients that died in that particular group?

DR. AGGREY: One patient died of septic shock related to necrotic enterocolitis. The second patient died of severe (inaudible) failure. The patient also had chromosome anomaly, and it was believed that severe pulmonary hypertension may have been related to the chromosomal abnormality.

DR. ANNE: Okay. Thank you.

DR. HUDAK: Dr. Cunningham?

DR. CUNNINGHAM: Thank you. Just one

clarifying. So in your literature summary in the limitations, if we look at the last one, the CONTEGRA were implanted over longer periods of time, that actually fortifies the data about less re-operation and explantation, but it does favor that, perhaps, the increased rate of endocarditis in the CONTEGRA, so. It was probably obvious to everyone else, but.

DR. PEIRIS: These are all very good questions and definitely worth considering and pointing out.

DR. HUDAK: Dr. Hoehn?

DR. HOEHN: Sorry. I had another question. We're all fixating on the Kido study. Was that an American study? I can't find it online. The one where half the people were reoperated and there's the 15 percent mortality.

DR. AGGREY: The Kido study I think it was from OMAN. That's an OUS study.

DR. HOEHN: It was where?

DR. AGGREY: OUS study.

UNIDENTIFIED MALE: Outside the U.S.

DR. AGGREY: Sorry, outside the U.S.

DR. HUDAK: Dr. Anne?

DR. ANNE: You know, I did not see any mention of, like, pseudo-aneurism reported in this particular, you know, the literature search and whatever else. Was that included as one of the other diagnoses by any chance?

DR. AGGREY: Yes. The papers did not -- as you can see, there are three papers for the pediatric only population and two papers for the adult and pediatric population, so it was only five studies. This number is small compared to what we presented previously.

The previous papers have reported (inaudible) and dilation. These papers did not report data on pseudo- aneurysm.

DR. SHWAYDER: I just had the simple question, is this placed with sternotomy or can you do it by endoscopic?

DR. PEIRIS: Sternotomy.

DR. SHWAYDER: Sternotomy.

DR. PEIRIS: The conduit can be minimally

dilated and potentially mitigated from replacement via transcatheter balloon, quote/unquote, angioplasty dilation.

DR. HUDAK: Okay. I think we're at a point where we can do a button vote on the FDA recommendation to continue current procedures with reporting in 2017.

Okay. We'll do a voice recording starting with Dr. Fischer.

DR. FISCHER: Gwen Fischer. I agree.

DR. MOON: Mark Moon. I agree.

DR. HAVENS: Peter Havens. I agree.

DR. TURER: Christy Turer. I agree.

DR. SHWAYDER: Shwayder. Agree.

DR. CNAAN: Avital Cnann. I agree.

DR. CATALETTO: Mary Cataletto. I agree.

DR. CAMPBELL: Jeff Campbell. I agree.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. HOEHN: Sarah Hoehn. I agree.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. I agree.

DR. WADE: Kelly Wade. I agree.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: Thank you, Dr. Aggrey. So conclusion, the committee does recommend unanimously continue current monitoring of the CONTEGRA device.

Okay. Next up is Pleximmune. Okay. Great. All right. I think we're ready. If you all could introduce yourselves down there.

DR. VELIDEDEOGLU: Ergun Velidedeoglu, medical officer. Division of Transplant and Ophthalmology Products, CDER.

DR. WIENEKE: Hi, good afternoon, Jacqueline Wienke, medical officer, Division of Chemistry and Toxicology Devices.

DR. LIAS: Courtney Lias, director of Division of Chemistry and Toxicology Devices.

DR. HUDAK: Okay. Dr. Kelm?

DR. KELM: Hello. Good afternoon. My name is Kelly Kelm and I'm the branch chief of Cardio Renal Diagnostic Devices in the Division of

Chemistry and Toxicology Devices. Today we'll be talking to you about Pleximmune.

This is our second time presenting, so last year was the first. So I think because IVDs are still novel for this committee that we sort of kept our brief overview of IVDs to present to the committee before we get into the regulatory history and information about the device and update you on the literature review and MDRs over the last year.

You may have already heard this from the previous presentations on HDEs, but for HDEs we're looking for probably benefit outweighing the risk of injury of illness from the use of the device.

So briefly, what is an IVD or in vitro diagnostic device? IVDs are reagents, instruments, or systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health in order to cure, mitigate, treat, or prevent disease or its sequela in man, and further, IVDs are also for use in the collection, preparation,

and examinations of specimens from the human body.

So as part of a pre-market submission IVDs must establish adequate analytical performance that supports the claims made in the intended use that the sponsor provides us. Sponsors should show that their device accurately measures the analyte and that it does so reliable and reproductively when taking into account all analytical steps of the assay.

In addition, they establish other device characteristics such as the lowest concentration of input sample that yields a reliable and accurate result. They assess whether any compounds interfere with the testability to generate an accurate result, and provide information on the methods for control and calibration of the assay, information on software, if there is any used within the device.

So sponsors should also establish the clinical performance or clinical validity of the test. The clinical performance may be based on existing clinical data, new clinical trial data,

or review of information in the literature. Lastly, IVDs have their own labeling regulations that require the package insert to include adequate instructions for use, the intended use, any warnings, limitations, and finally, instructions on how to interpret the test results and a summary of the analytical and clinical performance characteristics.

So most of the time a test's effectiveness for a particular intended use is expressed as sensitivity and specificity or as predictive value. Sensitivity tells you how likely the test is positive in someone who has the disease. Specificity tells you how likely the test is negative in someone with the disease. Sensitivity and specificity must be evaluated together as they are dependent on each other.

Similarly, we consider positive and negative predictive values together. Positive predictive value tells how likely someone is to have the disease if they have a positive result. Negative predictive value tells how likely someone

is to not have the disease if they have a negative result. Positive and negative predictive values are often preferred because the information is more reflective of the decision a clinician must make when they receive a lab report. Predictive values also depend highly on the prevalence of the disease in the population.

So here's the regulatory history for the Pleximmune test. It was granted humanitarian use designation of HUD back in June 2009. HDE approval was granted in August of 2014. I just wanted to note, there was no post-approval study for this HDE.

So we're going to present to you the indications for use for this test and it spans two pages, so bear with me. Pleximmune test is intended to be performed at a single laboratory to measure the CD-154 expression on T cytotoxic memory cells in patients peripheral blood lymphocytes. It is a qualitative prognostic test intended to be used in patients less than 21 years old with liver or small bowel transplantation.

It is an aid in the evaluation of the risk of acute cellular rejection or ACR, and must be used in conjunction with biopsy, standard clinical assessment, and other laboratory information. So this test is highly adjunctive and a clinician would not use this test alone, as said here, it's used with biopsy and other assessments that the clinician is performing.

I just wanted to reiterate that the aid in the evaluation of the risk means that this is a prognostic marker, so it's not necessarily use as a aid of diagnosis, but sort of a piece of information that a doctor would use when they're assessing whether or not a patient is at risk for ACR.

So the Pleximmune test is intended for use at the following time periods. So during the pre-transplantation period, the test can predict the risk of transplant rejection within 60 days after transplantation, and during the early and late post-transplantation period, for blood samples collected within 60 days after

transplantation, and for blood samples collected 200 or more days after transplantation the test predicts the risk of transplant rejection within 60 days after sampling.

So in both cases it's predicting 60 days after either transplantation or sampling, and we've underlined that because those are distinct. These time periods, we acknowledge the gap, is based on the data that was provided to us by the sponsor during pre-market review.

So here is a brief description of the Pleximmune test and what it is intended to measure. So here we've simplified in a picture the recipients immune response to donor cells, and this is the mechanism that the Pleximmune test is measuring. So the first event on the left is antigen sensing which is the presentation of the donor antigen to the T-cell by the antigen presenting cell.

The T-cell can either accept the donor antigen by undergoing apoptosis, in the top right, or can attack the donor by mounting a donor

specific inflammatory response. The Pleximmune test measures the inflammatory immune response of the recipient to the donor by measuring those T-cells which express the inflammatory marker CD-134, also known as CD40 ligand.

So the Pleximmune test is based on lymphocyte co- culture between recipient and donor peripheral blood lymphocytes. You also need to measure the background reaction which is the recipient T-cells which were expressed CD-134, and there's the reference reaction with measures recipient T-cells expressed CD-134 in response to simulation with other unrelated or third-party cells. So these three reactions are all measures by flow cytometry which is pictured in the bottom. And so you're looking for CD-134 expression in these three reactions.

The results of the Pleximmune test are an immunoreactivity index which is a ratio of the recipient's inflammatory response to donor cells expressed as a fraction of his or her inflammatory response to the third party cells.

If the donor-induced response exceed the response of the third-party then the individual is at increased risk for ACR. There are two cutoffs used. One for pre- transplant and one for post-transplant samples. Here's the description of the activity response and shows you the two cutoffs of pre- and post-transplant cut offs.

So here is the clinical evaluation study that was presented to us in the HDE. So a total of 122 specimens were evaluated from 87 individual pediatric transplant patients. Of these, 97 samples consisted of 33 pediatric pre-transplant subjects and 64 post-transplant samples from pediatric samples were also analyzable. This is a combination of 30 from the early post-transplant period and from the later post-transplant period. So here on one slide is the overall study results. But I'm going to walk you through them in detail in the next two slides. So this is the summary for the pre-transplant samples. So the test predicted correctly the increased risk of ACR

80 percent of the time and gave 20 percent false positive results. The test predicted correctly decreased risk of ACR 74 percent of the time, and gave 26 percent false negative results.

For the post-transplant samples which, as I said, was the early and late post-transplant periods together. The test predicted correctly the increased risk of ACR 64 percent of the time and gave 36 percent false positive results, and the test predicted correctly decreased risk of ACR 92 percent of the time, and gave 8 percent false negative results.

So this is the annual distribution number for this device is 4,000 tests per year. This is the actual device distribution over the period of time from June 1, 2015 to May 31, 2016. Plexicion informed us that they performed a total of 254 Pleximmune tests for a total of 210 patients at their laboratory. All of these specimens were post- transplant samples. They have them in testing on the pre- transplant specimens.

And as you can see among the 210 patients it was split fairly evenly amongst males and females, and then the average of these patients is 10.4 years with an age range from 4 months to 20.95 years old. Then we have the description of the type of transplants that they had received there at the bottom.

So we performed a literature review to look for potential safety issues for this test. We looked over the time period of June 1, 2015 to May 31, 2016. I have a description of the method up here in terms of where we looked and how we did the literature search.

Over this time period there were no publications that indicated any safety issues with the test. We also used two methods to try and identify if any adverse events or complaints were issued over this time period for Pleximmune. We did a search of the MAUDE or the new PRIMO database for the same time period, June 1 of last year to May 31 this year. You can see our search criteria here indicated for the brand name and

other key words. We did not find any MDRs.

We also received information from the sponsor, upon our request, that indicated that they had not received any MDRs or complaints over that time period.

So in conclusion, over the time period June 1, 2015 to May 31, 2016 Plexicion performed a total of 254 Pleximmune tests for 210 patients at their laboratory. A review of the published literature and MDRs since the time of approval and over the last year has not identified any new or unexpected risks for the pediatric population when compared to the pre-market data.

FDA concludes that the benefit risk profile of the Pleximmune for its indications for use continues to support the HDE for which the exemption was granted. FDA recommends continued surveillance and will report to following to the PAC in 2017: the annual distribution number, our literature review, and our MDR review.

So the question for the PAC is does the committee agree with FDA's conclusions and

recommendations? Thank you very much.

DR. HUDAK: Thank you, Dr. Kelm. So this is open for discussion. Dr. Hoehn?

DR. HOEHN: Sorry, I have another question. Sarah Hoehn. Was there a reason why it was only used for small bowel and liver transplantation and wasn't used for any other kind of transplantations?

DR. VELIOLEOLEOGLU: No, and I can't think of a specific reason why this wasn't used for other types of organ transplantations, but that was the study population. I mean, this may also turn out to be useful if it's tried in kidney transplantation, but I don't think we have data on that yet.

DR. HUDAK: So I do have a general question in terms of how well this has been received clinically. Just looking at the numbers you present, personally, if I were to look at a result I would have sufficient uncertainty as to what the result meant.

DR. VELIDEDEOGLU: Can you please

repeat the last part of your question? The last sentence?

DR. HUDAK: Yes. I was saying that depending what the result was, whether it was positive or negative, I'd be uncertain as to what it really meant. Because it could be positive and not be correctly positive. It could be negative and not be correctly negative. So how do people use this an synthesis this information into clinical care?

DR. VELIDEDEOGLU: Well, we had a similar discussion last year, and I fully understand the purpose of the question. In the transplant world, especially in the case of liver transplantation, the diagnosis of acute rejection may be very challenging at times. As you might all appreciate, I mean, if you give the same pathological specimen or the same slide to two different pathologists you may end up with different results. That's not often the base, but it may happen.

And in the case of liver

transplantation, especially among the many confounders, especially in the case of hepatitis C patients, sometimes even the biopsy may not be helpful. It may be very challenging to decide if it's recurrent Hep C or acute rejection. So what I'm trying to say is that it's the diagnosis of reject is arrived after considering multiple factors. The clinical course, the time point after transplant, the origin of disease, the results of other imagining studies, and, of course, the biopsy is considered to be the gold standard. But biopsy itself may sometimes be also be misleading, especially if it's a protocol biopsy performed in the absence of liver dysfunction.

So the main problem, one of the main issues in the transplant world now is how much immunosuppression is the right amount? And nobody knows the answer and that applies to all types of transplantation. So this adjunct tool is, I believe, I personally believe, is a step in the right direction in helping the efforts of defining

the optimum immunosuppression in these patients.

As specified on the label, it's never the main diagnostic tool. It should not be used as the main diagnostic tool, but I believe it's a useful adjunct, and it's -- we are hoping that it's going to developed further.

DR. WIENEKE: I'd also like to add we sometimes hear some feedback about how people are receiving tests. We don't have that type of feedback for this test. I think the only information we really have is that about 250 tests were ordered last year.

DR. HUDAK: So maybe, Dr. Kelm, could you bring up the slide again from the beginning about the pre-transplant numbers?

DR. KELM: For this year or for the original study?

DR. HUDAK: Whatever you've got.

DR. WIENEKE: Do you mean the predictive values?

DR. HUDAK: So the pre-transplant set, 33 --

DR. WIENEKE: And that's the top?

DR. HUDAK: Right.

DR. WIENEKE: Mm-hmm.

DR. HUDAK: So those numbers are, they are what they are, and that's my question, so I'm confused, but okay.

Yes?

DR. JONES: This is Bridgette Jones. For the post-transplant predictive values were you able to look at to see if the best performed better when measuring then early versus late post-transplant? Because initially you mentioned that can be measured, I think, 60 days and 200 days out. Does the test perform better depending on when you measure it?

DR. KELM: We looked at all of that during the review. I'm not sure we have that data with us. Let's see if I've got it here.

DR. WIENEKE: No. These presentation hasn't pooled.

DR. KELM: I don't recall whether -- that we saw a difference. Sharon, do you

remember?

DR. HUDAK: Please come to the microphone and identify who you are and who you represent.

DR. KELM: Unfortunately, we didn't prepare to present the pre-market approval decision information.

DR. MARFATIA: Yes, I don't know why, but I think there were no major differences and number of samples were very small to make that kind of (inaudible).

My name is. Shirin Marfatia

DR. HUDAK: You represent?

DR. MARFATIA: I was the lead reviewer when it actually was reviewed.

DR. HUDAK: Okay. You're with the agency.

DR. MARFATIA: Mm-hmm.

DR. HUDAK: Great. Dr. Turer?

DR. TURER: I wondered to what extent the response depends on what immunosuppressive drugs and what doses patients are on, so that, you

know, could the sensitivity and specificity change? Because you're looking at the recipients' inflammatory response to donor cells.

DR. LIAS: So when we have test come into us we do have them look at interferences, and part of that is that the -- we look at what the test is measuring and we assess, also, the patient population, and along with the sponsor, try to develop a list of potential interfering compounds. A lot of times we ask that they test drugs that the patient population would typically be on at the levels or a little, you know, maybe even higher levels to find out whether or not that might be likely to analytically interfere with the assay.

So that testing was done and we did not see significant interference. Now, that being said, part of the reason that we do surveillance is to try and find out whether or not there are new interfering compounds that are identified through, you know, real life testing. And we have not heard from the company that they've had any

scenarios where they've identified that yet.

DR. HUDAK: Dr. Cunningham?

DR. CUNNINGHAM: Thank you. So if the goal of using this along with the other clinical data is to either increase or decrease immunosuppression based on your worry about the risk of rejection, and the goals are to prevent rejection, but also to minimize immunosuppression and post-transplant lymphoproliferative disease wouldn't it help us if we're evaluating the safety of this test to know what those data are in relation to when this test is used?

DR. VELIOLEOLEOGLU: Are you saying that further safety evaluation needs to be done in the post-marketing setting? Is that what?

DR. CUNNINGHAM: Yes. Maybe I'm misunderstanding, but it seems like if we know the rate of post-transplant lymphoproliferative disease when this is and isn't used, graph rejection when this is and isn't used, if there's a higher than if we use this test of the clinicians use this test, and there's a higher

rate in this group of post- transplant lymphoproliferative disease doesn't it tell us that this test is sending them down the wrong road?

Wouldn't those data be important for us not to just analyze whether the test works, but in the clinical realm how it affects decision making, and then how it affects outcomes?

DR. VELIDEDEOGLU: Well, certainly it can be the subject of another clinical study, but as you have seen, the numbers are quite small, and we have only, like, 250 samples within the last year. And, in fact, the pediatric liver transplant patient population and small bowel -- pediatrics small bowel patient populations are quite small patient populations. But this can certainly be the subject of an upcoming study.

DR. CUNNINGHAM: And just looking -- go ahead.

DR. PEIRIS: I just want to, maybe, try to contextualize a little bit of this because these same issues came up in previous reviews, and

I think the concern is, you know, the decision that went into approving the device versus our current issue, (inaudible) safety of the device.

And when we think about the safety of a device of this nature we're thinking about the safety of utilizing this specific test. Not necessarily how it will be interpreted and what the management will be afterwards. That tends to get into that issue of the practice of medicine that always has that clear distinction. However, we, all being physicians, have been in that exact same situation where we wonder what is the pre-test probability before we order a test, and what will our decision be in terms of managing the patient after the test?

The FDA's responsibility was to figure out whether this test actually works the way that it's actually intended to work. The clinical and analytical validity of the test.

DR. CUNNINGHAM: Duly noted.

DR. HUDAK: Any other thoughts? If not we can bring up the question slide. So this has

been updated over the past year with additional information and the question is, does the committee agree with the FDA's plan to do continued surveillance and report again in 2017? So, use your buttons.

Okay. So we'll amplify with some verbal comments starting with Dr. Anne.

DR. ANNE: Premchand Anne. I concur.

DR. WADE: Kelly Wade. I concur.

DR. WHITE: Michael White. I agree.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. CUNNINGHAM: Melody Cunningham. I agree.

DR. CAMPBELL: Jeff Campbell. I concur.

DR. CATALETTO: Mary Cataletto. I agree.

DR. CNAAN: Avital Cnaan. I agree.

DR. SHWAYDER: Shwayder. Agree.

DR. TURER: Christy Turer. I agree.

DR. HAVENS: Peter Havens. I agree.

DR. MOON: Mark Moon. I agree.

DR. FISCHER: Gwen Fischer. I agree.

DR. HUDAK: Okay. Thank you, Dr. Kelm. Okay. We'll do another change out. We'll move on to the Enterra Therapy System.

Okay. For this discussion, I think Dr. Moon is recused. And the new people at the table are?

DR. VENKATARAMAN-RAO: My name's Prea Venkataraman-Rao. I'm a medical officer in the Gastroenterology Devices Branch.

DR. FORNAGER: My name's Ryan Fornager. I'm a chemical engineer and reviewer in the Division of Reproductive, Gastro Renal and Urological devices.

DR. MIN: Lauran Min, epidemiologist in the Division of Epidemiology.

DR. HUDAK: Okay. Thank you. Cathy, you have the floor.

MS. RICKETTS: Good afternoon, my name is Catherine Ricketts. I'm a nurse analyst in the Division of Post-market Surveillance in the Office of Surveillance and Biometrics at the FDA. I will

be presenting the summary of the results of the FDA's annual safety review of post-market data for the Enterra System.

Today's presentation will consist of this basic outline. Enterra consists of surgically implant neurostimulator, intramuscular leads, and an external clinical programmer. Enterra's indicated for chronic intractable nausea and vomiting, secondary to gastroparesis of diabetic or idiopathic etiologies in patients 18 to 70 years of age.

The annual distribution of Enterra during the last reporting period has not exceed the allowable ADN of 4,000. There were 103 neuro stimulators implanted in pediatric patients.

I will now present the summary of the results of our review of MDRs with a focus on the pediatric MDRs. Similar to last year's methods, the database search identified all MDRs related to the Enterra Therapy System, resulting in an initial results of 351 MDRs, 17 of which were pediatric patients, 112 MDRs were considered

indeterminate age reports because no information about the patient's age was provided.

This table shows the number of MDRs by event and age group. Of the original 351 reports identified, 35 were accounted as duplicate reports for a unique event. One MDR was excluded from this analysis since the event was reported in a journal article, discussed under the literature review of this presentation. Therefore, there were 315 unique events reported, zero deaths, 203 injuries, and 112 malfunctions. I'll be focusing on the 17 pediatric MDRs.

This table shows the time to event occurred in 129 MDRs, including 10 of the 17 pediatric patients. The pediatric time to event occurred were within the first year of implant and included lead erosion and pocket infections, return of symptoms and inappropriate shocking.

This table identifies the pediatric MDR occurrences of the most common problems, both patient and device combined, and clinical issues in comparison to last year's findings. Similar to

last year's complaints were electric shock or nerve stimulation undesired, nausea, vomiting, or complaints ill defined, and pain and discomfort. Each resolved with program adjustments and/or system replacements and attributable to high or low impedance issues commonly associated with battery depletions or lead malfunctions.

Different this year is the complaint of infections and erosion and device leads. However, root causes were not mentioned in the reports.

Overall, both patient and device problems observed for pediatric patients were similar to those observed for adult patients and for reports with indeterminate age. While these issues are known inherent risks for the device, and do not represent any new or previously unknown concern regarding patient safety, there were more issues of impedance this year directly related to battery issues and/or lead placement. In most instances, these devices were not returned for evaluation by the manufacturer.

I will now present a summary of our

review of the published literature. FDA conducted a systematic literature review on the safety and probable benefits of Enterra in the pediatric population. This is an update from the literature review presented at last year's PAC meeting.

The purpose of the literature review was to address the following questions in pediatric patients younger than 22 years of age. What are the probable benefits of Enterra for improvement in upper GI symptoms, reduction in the need for nutritional support, and improve gastric emptying time? What adverse events are reported in the literature after treatment with Enterra?

A similar search to last year's PUBMED and MBASE were conducted using the listed terms for Enterra, and limited to articles of clinical studies of pediatric patients published in English between May 1, 2015 and April 30, 2016, yielding 132 citations.

After assessment of the abstracts and full text articles for eligibility, two articles remained for full review and assessment. Reasons

for exclusion are provided in the executive summary.

I will start by presenting the results of the first included article. The study by Islam et al is a retrospective review and included 67 pediatric subjects with medically refractory gastroparesis implanted between 2004 and 2014 and followed for an average of three and a half years. The mean age was 13.7 with a range of 2 to 19 years,

percent were female and 85.6 percent were Caucasian. This study's probably benefit result of Enterra

included improved reports of symptoms, food intake, and reduced need for parenteral nutrition at 1 to 12 months compared to baseline, with a decreased follow up rate after the first 6 months. In 11 subject symptom scores could not be obtained.

The following adverse events were reported in the Islam study. Device explant in 10 patients for lack of symptom improvement,

improved symptoms which no longer required stimulation, intra matic disruption of the pocket, device replacement in 13 patients due to an expire battery, lead repositioning in five patients due to early symptom reoccurrence and long term failure of stimulation.

Lead erosion through that gastric mucosa in two patients, seroma development in one patient one month after device implantation, four deaths, three from progressive respiratory insufficiency, and one with no information provided.

The second paper by Hecker et al involved 151 GP patients, both pediatric and adult implanted with Enterra and followed for 12 months. This study did not, however, report data separately for pediatric and adult subjects.

The Hecket's study reported 75 percent of patients had improved overall symptoms, noted to be greater in diabetics than in idiopathic patients. With the greatest improvement in nausea, early satiety, and loss of appetite. Symptoms with the least improvement included

constipation, diarrhea, and abnormal distention.

The Heckert study did not report on changes in need of for nutritional support or gastric emptying time following Enterra placement. The Hecker et al study did not report an event occurred in a pediatric or adult patient because the age was not provided. The most common adverse event reported in 15 or 138 patients was pain or sensation at the stimulator site after placement.

Two diabetic patients had Enterra removed for infection. There as one death of a diabetic patient for unrelated causes.

The two studies included in our systematic literature review suggest improved upper GI symptoms after treatment with Enterra. Although the patients may require additional surgery. The effects on the need for nutritional support and GET are less clear. Our results for the studies should be interpreted in light of the following key limitations.

Our review included only two papers meeting the search criteria whose quality of

evidence was relatively low. The Islam et al study was a retrospective analysis focused on the pediatric population and subject to bias in which the true safety and probable benefits of Enterra may have been over estimated since it evaluated a select group of patients who had previously responded favorably to temporary treatment.

The Heckert et al study was a larger study of 151 pediatric and adult subjects. However, it was not clear if the reported benefits or adverse events were experienced specifically by pediatric subjects. For these reasons, we are limited in our ability to make any conclusions about the probably benefits and safety of Enterra in the pediatric population.

These findings are consistent with the results of the Enterra Systematic Literature reviews presented in the previous 2014 and 2015 PAC.

In conclusion, no new adverse event types have been reported in the MDRs or in the literature over the past year. Given the results

presented, the FDA believes that Enterra should remain an HDE device. We recommend continued surveillance and will report our findings to the Pediatric Advisory Committee in 2017.

Does the Pediatric Advisory Committee agree with our conclusions and recommendations?

DR. HUDAK: Thank you. This is open for discussion. Dr. Havens?

DR. HAVENS: It seems like this device has been on the market for quite a long time, if I understand what you said. Since 1999? And it's got a humanitarian device exemption which means that -- which I interpret to mean that finally when it gets shown to be useful it will bump out of this category as humanitarian use and actually get into the real world of real use. Am I missing something?

So then the question is, how long do you have to show marginal or no benefit before you stop being eligible for humanitarian use?

DR. PEIRIS: So, forever. You can actually stay within the HUD/HDE system. As Dr.

Nelson mentioned earlier, the device has been approved by the FDA. If the sponsor wishes to consider another pathway, such as PMA, they can certainly come to use for that reason. Unless they begin to have use above the ADN there is no current legislative regulatory authority that forces a manufacturer to actually -- or a sponsor to change out of the HUD HDE. The device is approved and continues to be available for as long as they would like within that pathway.

DR. HAVENS: Thank you very much.

DR. HUDAK: Dr. Hoehn?

DR. HOEHN: I have one question about the two cases between April of 2015 to May of 2016, about the two infection erosion cases. My two questions related to those two cases were. Number one, do we know if they had any comorbid conditions that put them at risk, and do we know what the interventions were for the erosion? Did they have to have the thing removed? Do we know what happened?

MS. RICKETTS: As far as I know, when I

was reviewing the MDRs I did not have information that told me whether or not they had any comorbidities that would have made them at risk for that. I do believe that for the infections they were -- the devices were usually treated with aggressive antibiotics.

I think, if I remember right, there might be one where they actually took the device out and replaced it, but most often it was just the aggressive antibiotic treatment. There really wasn't any report of whether or not there was resolution behind that. It was just that's the -- that was the treatment.

DR. HOEHN: Yes, specifically I wondered if there were any long term negative effects to the erosion? Because, presumably, you have to do something more than antibiotics if it eroded through the skin.

MS. RICKETTS: Right. With the erosion cases, more often than that those leads that were eroded were taken out and replaced. You know, that was the only -- that's as far as they gave us

with what happened afterward.

DR. HOEHN: Okay.

MS. RICKETTS: As far as follow up.

DR. HUDAK: Dr. Anne?

DR. ANNE: With regards to the four deaths that you saw there, you know, three of which are progressive respiratory insufficiency. Was that due to some other comorbidity or was that associated with somehow or other with the Enterra implantation?

MS. RICKETTS: The three deaths that you're referring to were reported in the Islam et al paper, and they provided very limited information on those stats. The only information that we have are that the three patients died of progressive respiratory insufficiency. Two are post lung transplant and one had severe cystic fibrosis.

The paper also noted that Enterra had provided relief of their GP symptoms prior to their death. That's the only information that we got.

DR. ANNE: Okay.

DR. HUDAK: Dr. Cunningham?

DR. CUNNINGHAM: Just one other quick thing. So we've reviewed this a number of years in a row and it's been fine. Remind me, do these have to be reviewed annually? Is that our mandate? Okay.

DR. HUDAK: Okay. Any other question? Comments? If not, we can proceed to vote with the buttons on the recommendation to continue the present course with monitoring and reporting.

Okay. So I think we'll start, Dr. Fischer, with you.

DR. FISCHER: Gwen Fischer. I concur.

DR. HAVENS: Peter Havens. I approve.

DR. TURER: Christy Turer. I concur.

DR. SHWAYDER: Shwayder. Approve.

DR. CNAAN: Avital Cnann. I concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. CUNNINGHAM: Melody Cunningham. Concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. DRACKER: Bob Dracker. I concur.

DR. WHITE: Michael White. Agree.

DR. WADE: Kelly Wade. Concur.

DR. ANNE: Premchand Anne. I concur.

DR. HUDAK: Okay. Recommendation is to continue the current monitoring and reporting. Thank you, Cathy.

I guess we come to the last presentation of the day on the Elana surgical kit. We have some new folk coming.

DR. ANDERSON-SMITS: Might just be me.

DR. HUDAK: Might just be you?

DR. ANDERSON-SMITS: Yes.

DR. HUDAK: Okay. You've got good back up there. All right. So if it's just you, Colin, you can get started.

DR. ANDERSON-SMITS: Last one and the shortest, so you guys are in the home stretch. Good afternoon. My name is Colin Anderson-Smits and I'm the branch chief of Epidemiology, Office of Surveillance and Biometrics at the Center for

Devices and Radiological Health. I'll be presenting the annual update on the Elana Surgical Kit.

Since the last PAC meeting a year ago, there has been no reported sales or use of this device within the U.S. There have been no MDRs reported in the past year associated with Elana, and there have been no peer review publications studying the use of Elana that involved human subjects since the last PAC meeting.

As a result, the FDA has identified no new safety concerns since the last year's PAC meeting. The FDA concludes that the probably benefit risk profile of Elana for the pediatric population continues to support the HDE. The mandated post-approval study has been placed on hold due to nonuse over the past few years within the U.S.

The FDA will continue to monitor sales and use, and should device use resume the mandated post-approval study will be reinstated.

The FDA will continue surveillance and

report the following to the PAC in 2017, an updated MDR review, an update of the mandated post-approval study status, and results, should the study be reinstated, and an updated literature review.

The PAC will now be asked the following. Does the committee agree with the FDA's conclusion and proposed approached?

DR. HUDAK: So I do believe this is a record.

DR. ANDERSON-SMITS: I did it last year too.

DR. HUDAK: We did last year too? Okay. Well, anyone have any questions, other than the obvious, why?

DR. SHWAYDER: Why what?

DR. HUDAK: Why --

DR. ANDERSON-SMITS: Why is there no use?

DR. HUDAK: Why are we discussing it?

DR. NELSON: The legislation says annual review. We are in conversations about whether we

can develop flexibility in the device arena, but those conversations are ongoing. But, basically, the way the legislation was written is it requires annual review by the PAC independent of the data at this point.

DR. HUDAK: Dr. Nelson, if you have devices like this that come up and there's absolutely no use or activity --

DR. NELSON: I'm not saying it's rationale. We're discussing whether there are ways we can discussion some flexibility like we've applied in drugs, but that's a continuing conversation.

DR. HUDAK: So my question was, why is there no use?

DR. ANDERSON-SMITS: Well, I'm not a pediatric neurosurgeon, but I would say that hypho bypass surgeries have just become obsolete. Most of them are treated endovascular these days.

DR. PEIRIS: This is one of those key issues in the pediatric populations and small populations where when new therapy has come about,

even when a device is approved based off of historical data, and the time that it takes to collect that data, by the time of approval and then marketing, whether that therapy still remains the most optimal therapy. And others may have already leap frogged about that therapy. So this is a classic example of that.

DR. HUDAK: Okay. Just wanted to get that in the record. Okay. So I think there are probably no other questions. We will press the buttons and go around the table.

DR. SHWAYDER: Show me the question one more time on the slide before.

DR. HUDAK: It happened so quickly you didn't take it in, I know.

Okay. We'll go around the table, and Dr. Anne, you have the honors.

DR. ANNE: Premchand Anne. I concur.

DR. WADE: Kelly Wade. I concur.

DR. WHITE: Michael White. I agree.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. Concur.

DR. CUNNINGHAM: Melody Cunningham. Concur.

DR. CAMPBELL: Jeff Campbell. Concur.

DR. CATALETTO: Mary Cataletto. Concur.

DR. CNAAN: Avital Cnaan. Concur.

DR. SHWAYDER: Tor Shwayder. I concur, but I'd add if there's no more sales next year you put it on some sort of suspension notice.

DR. ANDERSON-SMITHS: Can you repeat the question? I'm sorry.

DR. SHWAYDER: I had said, if there's no sales in the next year that you just put it on suspension and not waste the committee's time with it in the future.

DR. NELSON: We don't plan to. We have options on mind.

DR. TURER: Christy Turer. Concur.

DR. HAVENS: Peter Havens. Concur.

DR. FISCHER: Gwen Fischer. Concur.

DR. HUDAK: Okay. So the summary for this is that we agree with your continued observation of a null set.

So we've come to the end of the meeting we have done, I think, nine drugs and two vaccines, and five devices, and heard a couple other presentations. I think I would be remiss if I didn't once again note that I think the process of providing the information and interpreting it and summarizing it by the FDA and the committee has been superb once again, and very efficient meeting and presentation, and thank the committee for some unanticipated, but excellent insights into some of these drugs and biologics.

So I think with that, Skip, you want to have a final word? I think that Marieann might have an annoncement about some things for tomorrow, transportation and all that. Just to make sure.

DR. NELSON: Yes. I just wanted to remind, for those of you who are members of the committee and will be staying for the next two days, I guess Euneka’s meeting folks at 6:30. Part of the reason for that is you're not getting any special privileges to get through security,

and they won't -- you know, so you'll get in line and we want to make sure you're in line in time to actually get to the meeting room in time to start the meeting. So that's why an early time. The meeting starts at 8:00.

Just for those who are not invited, I mean, just explain that so it's not like the in crowd and, you know, you're not part of the in crowd. This is a three committee meeting to look at opioids. When there's three committees around the table, generally, unless you have special expertise in opioids they invite the regular standing members of the committee and not those who are invited as special SGEs for the purpose of a specific drug or device review. So a number of you are standing members of the committee, a number of you are not, so that's what it's a function of. It's not that we have, you know, the cool kids and the uncool kids that we invite. Just to explain that process in case you were wondering.

But thank you very much for the day and

I think it's been a productive discussion. Marieann, I don't know if there's anything else you have to add?

DR. BRILL: Yes. I just want to say please check your emails. Euneka has reserved a van and the van will be downstairs tomorrow waiting for you. Please be there no later than -- or please be there between 6:30 and 6:45 a.m. Once you get into White Oak, Shivana and Sheila will be waiting for you as well so that they can show you where you're supposed to go.

So hopefully this will be a seamless process. Thank you.

DR. HUDAK: So just to amplify, they say that the van will depart exactly at 6:45 and there is a $30 roundtrip cost. They prefer cash. Just forwarding.

Okay. So I think we're adjourned. Thank you.

(Whereupon, at 4:23 p.m., the PROCEEDINGS were adjourned)

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CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the Commonwealth of Virginia

My Commission Expires: November 30, 2016

Notary Public Number 351998