PEDIATRIC ADVISORY COMMITTEE MEETING

Hilton Hotel & Executive Meeting Center
1750 Rockville Pike
Rockville, MD 20852

September 12, 2017

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WELCOME AND INTRODUCTIONS

DR. WADE: We're going to go ahead and start this meeting on time. I'm Kelly Wade from Children's of Philadelphia. I have the pleasure of pitching with Dr. Hudak today who's giving updates from Florida. And mostly I just want to start by welcoming everyone to this September meeting of the PAC, thank everyone for serving on this committee. There is one reminder this morning which is that there is lots of food in the walkways as we approach this room, but that is for other conferences, not for us. So, walk politely and keep walking.

As always, we will start this morning by going around the table and introducing us. This is a smaller group than yesterday. Dr. Jones, let's start with you.

DR. JONES: Good morning. I'm Bridgette Jones. I'm an allergist asthma immunologist and pediatric clinical pharmacologist. And I'm the pediatric healthcare organization representative from the AAP.

DR. CAMPBELL: I'm Jeff Campbell. I'm a pediatric neurosurgeon from Nemours.

DR. TURER: Christy Turer. I'm an internist, pediatrician, and obesity medicine physician from UT Southwestern.

DR. FISHER: Gwen Fischer. I'm a pediatric ICU physician from the University of Minnesota.

DR. HAVENS: Peter Havens, pediatric infectious diseases, Children's Hospital of Wisconsin and Milwaukee.

DR. CUNNINGHAM: Melody Cunningham, pediatric hematology, oncology, and palliative care physician, University of Tennessee, Memphis.

DR. CATALETTO: Mary Cataletto, pediatric pulmonology, NYU Winthrop in New York.

DR. WHITE: Michael White, pediatric cardiologist and IRB chair from Ochsner Clinic in New Orleans.

DR. NEVILLE: Kathleen Neville. I'm a pediatric hematologist, oncologist, and clinical pharmacologist at Arkansas Children's.

DR. CALLAHAN: David Callahan. I'm a child neurologist at Washington University, St. Louis.

DR. BRILL: I'm Marieann Brill. I'm the DFO for the Pediatric Advisory Committee.

DR. WADE: Kelly Wade, neonatologist from Children's Hospital of Philadelphia.

DR. MCGOUGH: James McGough, child and adolescent psychiatrist from UCLA.

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

DR. HOEHN: Sarah Hoehn, pediatric ICU and pediatric palliative care, University of Chicago.

DR. COPE: Judy Cope, Office of Pediatric Therapeutics, medical officer.

DR. QUINTO: Kenneth Quinto, Medical Officer at the Office of Pediatric Therapeutics at FDA.

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

DR. HAUSMAN: Ethan Hausman, Medical Officer, Division of Pediatric and Maternal Health.

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

DR. LEVIN: Bob Levin, Medical Officer, Team Leader at Division of

Pharmacovigilance, FDA.

DR. WADE: Great. And if we could have one more introduction on the left.

DR. SAYEJ: Wael Sayej, pediatric gastroenterologist, University of Connecticut School of Medicine.

DR. WADE: Welcome, everyone. I will now turn the microphone over to Marieann Brill for her opening statement.

OPENING STATEMENT

MS. BRILL: Thank you and good morning. The following announcement addresses the issues of conflict of interest with regards to today's discussion of reports by the agency as mandated by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. With the exception of the industry representative, all participants of the committee are special government employees or regular government employees from other agencies that are subject to the federal conflict of interest laws and regulations.

The following information on the status of the Advisory Committee's compliance with the federal conflict of interest laws including, but not limited to: 18 USC Section 208 of the Federal Food, Drug, and Cosmetic Act is being provided to participants at this meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts when it is determined that an agency's need for particular individual's services outweighs his or her potential financial conflict of interest, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the meeting topics listed in the meeting agenda, members and temporary voting members of this committee have been screened for potential financial conflicts of their own as well as those imputed to them, including those of their spouse or minor children, and for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of pediatric focus safety reviews for the following products: ABILIFY, KEPPRA, and KEPPRA Extended Release, CONTEGRA, ENTERRA, Pleximmune, and Elana.

This is a particular matters meeting during which specific matters related to the products previously identified will be discussed. Based on the agenda topics, and the analysis of the financial interests reported, FDA has determined that members and temporary voting members of this advisory committee are in compliance with federal ethics and conflict of interest laws under 18 USC Section 208. To ensure transparency, we encourage all voting and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

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

Ms. Amy Celento is participating as a patient family representative, which is a voting position.

We would like to remind members and temporary voting members that if the

discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement. The exclusion will then be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with the firms that could be affected by the committee discussions. Thank you.

DR. WADE: At this time I would just like to confirm that Dr. Portman is on the phone.

DR. PORTMAN: I am here, Kelly.

DR. WADE: Wonderful. Thank you. I will now turn the microphone over to Dr. Nelson for the introduction and agenda review.

OVERVIEW OF AGENDA

DR. NELSON: Thanks. And let me start off by thanking Bob yesterday and Kelly today for stepping in for Mark. I do have information from Mark. He stayed behind. As you know, he has responsibilities and apparently had to evacuate their NICU from the Children's Hospital. Where he says the only egress into the building was by boat for a while given the storm surge, but they were able to get them all transferred prior to the power going out in the building that they had been in, which was good. And personally, his house is fine and he's on high ground, so that's good news. And he wishes us all well. So, our thoughts and prayers are with Mark and the people of Florida.

Today we have a couple of presentations. I'll give one in just a moment, and then Ann McMahon will talk a little bit about Kidnet and get your thoughts on that program. And we have two drugs and five devices for our usual post-marketing safety review activities. And that pretty much takes us through to the noon hour. Not much else to say about the agenda. I won't say much about the safety reviews. You'll see an overview of the PAC, that I call the

State of the PAC, hopefully without too much pretention, but I will go ahead and give that if that's all right.

STATE OF THE PAC

DR. NELSON: I wanted to take this opportunity to sort of review where the PAC has been and where we see the PAC going, partly to introduce some changes we're planning to institute with the March meeting and devices, but to give you a broad overview of what we've been doing over the last now almost 15 years. I want to review the involvement of the PAC, primarily in pediatric-focused safety reviews and reports over the past, now almost 15 years, summarize our efforts to make more effective use of both FDA and PAC resources. And then to suggest a proposed plan for future engagement in pediatric pharmacovigilance.

So back in 1997, FDAMA included the Best -- the Better, I should say -- interesting, it went from Better to Best -- Pharmaceuticals for Children Act, which was the Act that initially started the activities around getting exclusivity, with additional six months marketing exclusivity for studies that were done in response to an FDA written request. This was renewed in 2002, as the Best Pharmaceuticals for Children Act, upgraded from better. And also in that act established the FDA Office of Pediatric Therapeutics. And basically, at the time, there was a Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, which at first met in 1999. And of historical interest, Mark Hudak was at that first meeting. I was not. I was only at the second. So, I think we're probably the two people who have been involved for the longest in this activity, but historical note.

FDA is unable to establish new advisory committees because there was a budget rule that didn't allow us to do that unless it was by statute. And so PREA -- which is the

regulations where FDA can require sponsors to do studies on the indication itself -- was enacted in 2003. And that established the Pediatric Advisory Committee as part of PREA. And the first meeting of this advisory committee happened in September of 2004. So that gives us almost 15 years, but if we wanted to count the previous subcommittee we can go longer.

Now, in 2007, FDAAA, the Food and Drug Administration Amendments Act, reauthorized BPCA and PREA until 2012. These are our usual, every five years, reauthorization of user fees. And 2017, so you see 2007, 2012, 2017. So, these vehicles have been appended to the user fee legislation.

This is what gave us explicit authority to label the product. Prior to that, we had to negotiate labeling, but basically this said regardless of whether the drug is safe or effective, there needs to be labeling. So that could include that the results were inconclusive, but there needs to be labeling.

It continued for BPCA, but then extended to PREA, including biologics and vaccine, the adverse event reporting requirement during the one-year period following a labeling change. So, prior to 2007 all of the pediatric focus safety reviews the PAC did was only for BPCA studies under exclusivity. Following 2007, it included PREA. It extended the Pediatric Advisory Committee through October 2012. And by adding PREA, and requiring pediatric labeling following studies under PREA and changing the PAC review to any pediatric labeling, as you can imagine, this increased the number of reviews that must go to the PAC. And I'm going to show you that data in the next slide.

As you can see, starting off in 2003 and 2004, it was fairly low. And basically, you had an increase with FDAAA in 2007, up to a peak. I remember one meeting where I think they did 19 products in one day. I mean, it was just insane. I mean, by the end of that day your mind was mush. I don't know if anybody else was at that meeting other than me, but it was a long day. And we just said no more.

And so, what happened at that point was that the Office of Pediatric Therapeutics agreed to cap the number of products per meeting so that everybody could at least remember what's going on by the time we got to the last product. But we also went from three to two meetings because of budgetary issues. And also with three meetings a year, we were doing two meetings at a time and it was very difficult for staff meetings.

Well, as you can imagine, the results of that change with the increase in labeling as well as the decision to cap the number of reviews per meeting. The number of products, then awaiting PAC review, beyond 21 months of pediatric labeling change. So, we have to review after 18 months. Then we let the data mature for 3 months. If you look right at 18 months, you don't have 18 months of data. We've picked 21 months as the arbitrary time to say we're behind. But as you can see, there's an increasing backlog of products for review precisely because we've capped the number of products going to the PAC at that time. And we thought this was a problem to be addressed.

Now, at the same time, the Pediatric Medical Device Safety and Improvement Act of 2007, came into FDAAA as well. This is the act that allows a manufacturer of a device to sell it for profit. So, HUDs are not allowed to sell for profit, but they -- and stimulating pediatric device development is very difficult. And this is an attempt to try and do that, whereas they would allow profit for devices that have a pediatric indication.

Now, as part of this, they said, well, let's have the PAC then review the safety of those devices and the appropriateness of that profitmaking. And so, we ended up with two things, and this is an important distinction. We ended up with the idea that the appropriateness of this exemption needs to be evaluated on an annual basis. And then the adverse event reports could be provided to the committee on a periodic basis. And our proposal, that I'll present to you later on, is to leverage this annual and periodic to basically take products that do not have a safety concern, and post them annually to the web like we're doing with the low risk drugs, and

then only come in with periodic safety for devices when we need to do that. And this was scheduled to sunset in 2012. But, as you can imagine, this also then increased. Here's all the devices up here. And so basically more work and more work and more work.

We also looked at the presentations. And as you can see here, this is the initial presentations. And so, this annual requirement meant we would present something initially after it got its HUD designation for profit. And then we had to present it every year. And the red shows that every year.

Now, the red, you would think it ought to get bigger, but there's -- as you will learn today and as you may recall, I think, one or two meetings ago, there was a device that went from HUD to PMA and received its full approval, which means it's no longer an HUD. Then it gets taken off the table, which is why the repeats got lower. You'd think they would just naturally get bigger. And often the repetitive annual presentation is of limited value and we can discuss that.

In 2012, we got FDASIA. What was important here was that BPCA, PREA, and the PAC are now permanently reauthorized. There's no sunset. So that was very important so that it provides continuity, it provides certainty. We don't have to renegotiate it every five years. It continued the FDA authority to label a product regardless of whether it was demonstrated to be safe and effective so that any studies under PREA or BPCA get into the label, which is important for transparency. It modified the adverse event reporting requirement from 1 year to 18 months, which you've already seen the backlog up over 21, so that's a pyrrhic victory, I guess. It allowed us to say we were no longer behind on products between 12 months and 18 months.

It did give us the authority to grant an extension of the due date for deferred pediatric studies. We haven't talked much about that, but there is -- unless you start a pediatric study pretty soon after adult marketing, or even before adult marketing, the odds of concluding

that study and getting that study done begin to fall off. And so, there's a number of post-marketing pediatric requirements under PREA that have dates that need deferrals. And we will give deferrals if we think there's legitimate reasons for the need for an extension. But if we don't think that's legitimate, we would then write a non-compliance letter. And both of these letters are publicly posted. And I'll come back to this in a later slide. It also reauthorized the HDE profit exemption until 2017. So that was FDASIA in 2012.

Now, so over the years we've introduced different approaches to the presentation and review of adverse event reports in order to better use FDA and PAC resources. And I'll show you a slide with the data, courtesy of Ken Quinto, I should say. But in 2006, we introduced abbreviated reviews. In 2010, we introduced justified abbreviated reviews. So that was where -- for example, the HIV drugs -- where there's going to be a certain number of deaths related to the disease.

In 2012, we introduced the designated abbreviated review. That's where it was an abbreviated review, but we thought we only needed one person to look at it. You might remember that, of those of you who have been on the committee. The purpose of that was mainly to reduce the conflict of interest work on our staff because we had to do conflict of interest for everybody on all the products, and we didn't think that was terribly useful.

And then in 2016, we introduced web-posted reviews which were initially for CDER products, but we have expanded that to CBER products in 2017, using the same criteria. We didn't think that was terribly controversial to do that. I believe -- is there one this meeting that's a CBER product or is that -- there's two. Two that are CBER products that will be posted. The FR notice is a little delayed. Ken, why don't you speak about that.

DR. QUINTO: The Federal Register has already been posted. The docket is scheduled to open up October 9th through the 20th. Due to the recent administration changes, the FR notice got in a little bit later and took a little bit longer for clearance than I thought. So,

unfortunately, as I usually have the docket open two weeks where the PAC meeting is open, unfortunately, it's going to open October 9th through October 20th. I apologize for that and will make sure next meeting that it will open during the PAC meeting. But currently there are 11 CDER products that are web-posted and 2 CBER products that are web-posted.

DR. NELSON: Thank you, Ken. And to be clear, I mean, the reviews get posted when the reviews are available. We open the document around the time of the meeting. But in this case because of the clearance process going from four weeks to seven weeks, it's not at the same time.

But here is the presentations. So, as you can see, we started off the abbreviated, and then added in the justified abbreviated, the green, and then added in the designated abbreviated review in the purples. And then moving to web posting, I think you can see that basically we're web posting a lot of the things that were previously in those sort of abbreviated presentations. And so, you know, increasing use of this and then a transition to web-posted reviews. And the purpose behind this is to try and make sure that what you are presented and talk about is actually worth talking about.

Now, this is a graph that shows -- these are the current CDER products that are on our database where they've had a labeling change and it shows you the number, that at this point are less than 18 months, so they're not quite mature. The number between 18 and 21 months, which it looks like it's about 8. And then shows you what I presented in the previous line graph, the number that are out above 21 months, at this point, which we'd consider delayed.

Now, FDARA 2017, which was signed into law on August 18th, did not make any changes in the reporting and review requirements for pediatric adverse events. So basically, everything remained the same for PREA and BPCA as I presented it.

What's interesting is in the oncology area there is an important extension of PREA to a molecular target. So, you can have the same molecular target in a pediatric cancer that you

have in adult cancer, but the indication could be different. And PREA tied to the indication meant that PREA could not be used for those pediatric oncology indications. So, it has that language.

What was also interesting, all of those pediatric oncology diseases are orphan indications and so it also included an exemption. You know, PREA, if you have an orphan designation you're exempt from PREA. It removed that for the pediatric oncology indications. What that means too is now all of those PREA labeling changes will be on the table for coming to the PAC. So, more. Whether that's necessary or not, I mean, who knows, we'll see. Because that's just happening now, so stay tuned for three years from now as we begin to see labeling changes potentially as a result of those studies.

Now, what's also interesting is what was putting into FDARA, was it requires FDA to inform the PAC of non-compliance letters for deferred pediatric studies and the responses to such letters. Now, the purpose of this requirement is not clear, although I asked our academy representatives whether they had any insight into this. And part of, I think, the motivation was if we think there's something that needs to be discussed about reasons behind pediatric deferred studies, and why they're delayed and non-compliant, this at least gives us the potential leverage to say we're going to take that and have a discussion at the PAC about whatever those issues may be. At the moment, there are no issues on the table for that. It also reauthorized the HDE profit exemption.

Now, the PREA non-compliance letter are posted. The Center for Biologics has two that they've posted. Here's the web link. Cedar has 28 that they have posted. So clearly, we're not going to screen you for 28 products for conflict of interest to have a discussion here of those 28 letters. But the websites list the sponsor, the product, it has a copy of the non-compliance letter. It has a copy of the sponsor's response if available. There's a few that are not available. And it has a status of the pre-requirement, either released, which could happen

afterwards, replaced by some other requirement, or potentially fulfilled. It could have been out of compliance, but then later completed the study. All of those are posted on the web, and so I might say at this moment, although I'm not sure what the implementation date is for FDARA 2017, please consider yourself informed. Anyway, so we've met the letter at least, maybe not the spirit.

The HUD PAC presentation proposal, and we've had a lot of discussions with both CBER and CDRH about this. So, again, the PAC reviews pediatric humanitarian use devices that have been granted an exemption to sell the device at a profit, meaning they can, if they have that. The statute provides for two aspects of PAC review; periodic, meaning as needed review of HUD adverse event reports, and annual review to ensure that the product still meets the HDE designation criteria for profitmaking pediatric use.

Now, it's interesting in that annual review, as you know, we still look at the safety. So, it's not as if we're not looking at the adverse events as part of that annual review, but for some reason there's also this language in there about pediatric. And there's no further specification, other than the language I just gave you, about the nature, content, and frequency of these PAC periodic review of HUD adverse events.

And so, what we're proposing is to learn from the drug experience and to say if, with that annual process of review, which we will still do, there are no safety concerns with a device -- no new safety concerns -- with a device, that that would be web-posted as we're doing with existing drugs where there are no safety concerns. And then if there are new safety concerns that would fit under the periodic presentation of safety issues, then we would bring that to the PAC.

So, that is the idea and our proposal is to institute that for the March meeting, which to point out I think would effectively, if we had done that for this meeting, all of the devices would probably have been web-posted. But I don't think that's a problem personally

and I'll go into why.

What do we see as the future? We're trying to optimize the use of both FDA and PAC resources. And so, on the device side, I know how much time they spend agonizing and developing their slide presentation. So, at the very least, to go to web posting means they no longer have to have that stage fright and agony of developing slides. Not everybody is sort of as comfortable with that as academic clinicians may well be.

Web posting annual device reviews absent a new safety concern that warrants PAC discussion. So, continuing to engage PAC in other advisory committee activities. One of the challenges in my mind, is to really use this group to advise the Agency on pediatric issues that are important. So, you all know you've been polled for potential availability at a future meeting. I'm hoping it occurs at that time, because there's some issues as to whether the material will be in from the sponsor in order to make sure it doesn't get delayed. But that meeting will happen if it doesn't happen on the day that you were polled. I can't say what that meeting is about because it's not been made public, but I will say it will be the first time that the PAC has ever been involved in this type of meeting, in 15 years, the first time, all right. So, it will be precedent setting.

We're in discussion with another division about the March meeting, and being able to actually look at a particular clinical trial scenario for a rare disease population, and have an open public session about the design of those trials, the appropriate clinical outcomes and so on. And then have a closed session about the particular IND. And so that's something we're in discussion.

We've had those types of meetings, I think, one or two times in the past. That's the kind of thing that we're thinking about getting this committee involved in more, and looking for those opportunities. Those opportunities had been going on in the past, but you guys have been so busy doing all of these safety reviews that there's been no time to do it. And so, the

hope is that as we clear more agenda time, while continuing to meet the legislative requirement to look at the safety, have the web posting for review, that then this committee can be engaged in conversations that would be much more impactful, if you will, on agency decision-making.

Now, we are adjusting some internal processes to try and eliminate the product backlog and we're tracking that. It's too early, at this point, to say whether we're being successful, but we're doing that.

And then the final one is to explore alternatives to the current time-based labeling-based pediatric focused safety reviews. So right now, we're looking only at the pediatric products that are labeled after BPCA and PREA and we're doing it based on time after labeling. And so all of the products that are not studied under PREA and BPCA, but there are many pediatric products that come in on their own, are not part of this. And so, the idea is to -- you know, some of you know we're having an Advancing the Development of Pediatric Therapeutics (ADEPT) workshop on big data in a couple of weeks. So the idea would be to have the next ADEPT workshop in 18 to 24 months be focused on pediatric pharmacovigilance, and as the question, what's the best way to do it.

At this point, I don't have a suggestion, but that would be the idea. A public workshop, bring in all the various stakeholders and experts. You know, the beauty of a workshop is you don't have to screen people for conflict of interest. You can get everybody together. Then the idea would be that there'd be a very draft sort of thought piece of what that might look like, which would then come back to a PAC meeting following that workshop. And then there could be a discussion, with advice among the PAC members, about what we think we ought to be doing if we replace this time-based, labeling-based system.

And then part of the idea there for this timing is in 2022, would be the next user fee legislation; so that it would be teeing up the possibility if we needed to make legislative changes to do that, that those could be at least discussed. Although, strictly speaking, the FDA

only provides technical advice about legislation, and does not recommend legislation. But, so that's the idea and that's sort of where we've been, where we are, where we might see ourselves going. And I'm happy to entertain any questions if time permits.

DR. WADE: So I'll open the floor. We have a few minutes for questions.

DR. NELSON: So, clear.

DR. WADE: Okay. I'll ask one.

DR. NELSON: All right.

DR. WADE: In my recollection, as we review safety data here at the PAC, there often is a question at the end where we vote and say do you agree with this recommendation made by the staff who have produced the report. And so, I'm wondering in that metric of the graphs that you showed, what fraction of the time does the PAC agree with the recommendation. Because I think that gives data credence to this idea of moving these reports online.

DR. NELSON: Ken.

DR. QUINTO: I looked at sort of the data looking at that specific metric. What I was looking for was the times the PAC recommended labeling changes. And it was less than 10 percent of the time for all the products going back to 2006. I can't remember the specific number off the top of my head, but it's much less than 10 percent.

DR. NELSON: I think it was about 36 or 37, something like that, so it's a fairly low number. And that doesn't capture whether the PAC agreed or disagreed. Because FDA may well have recommended a labeling change that the PAC agrees with. And, you know, part of the challenged, just as an aside, and thinking about pharmacovigilance, I mean, there are some examples -- I think AndroGel is an interesting one -- where there's been important adverse events that are not captured by frequency; but where you had inadvertent transfer from men to infants because of skin contact with virilization, even with one child needing surgery because of

mass immunization and stuff.

And in my own mind, I don't have a conception of what a different approach of pharmacovigilance would look like, but the signal to noise ratio here is quite high or quite low, I should say, so.

DR. TURER: I wonder two things. It would be helpful to understand what the sponsors are collecting in the course of their studies and whether there are standard metrics that should be collected in all children, for example, weight and height, to allow, you know, tracking of BMI. Whereas, a lot of studies right now are using just self-report of certain adverse events. And I think it would be helpful to understand how sponsors collect this information and how determinations are made about what they track.

The second thing is I really want to attend that data meeting. Unfortunately, I think it's going to be challenging, given its separated in time from this meeting. But the ability to track information about drugs used in children over time into adulthood. And I hope that meeting will address it. And if it's going to be available online, I'd like to be able to attend remotely. But I think that that's a really important thing to consider when we're talking about pediatric drugs, because the exposure time and the possibility of developing adverse events can be disconnected from the providers who were seeing those kids. Aka, pediatricians prescribe them, but we don't see the adverse events until they're being followed by internists.

DR. NELSON: Yeah, I guess two comments, and thank you for those observations. The first is I think the ADEPT meeting is going to be webcast; and so I'll ask for our office to make sure we circulate to the members of the committee the webcast information. And second of all, I could imagine part -- I mean, again, we'll put together a working group, we'll plan this workshop. But I can imagine one part of this pharmacovigilance strategy would be to look at the drug across its life cycle. And so, what you choose to look at after the pediatric studies are completed, I think would be related in some way to what you've seen in the clinical

trials.

And so, your question about having a clear understanding of what the data are in the pre-pediatric labeling space for the collection of safety data, around particular products, I think could be woven into that discussion. Because I think post-marketing, done rationally, would build on what's been seen in the pre-market. I say premarket in a pediatric sense because it may well be marketed for the adults, but pre-pediatric labeling based on the pediatric studies.

DR. WADE: I just would second what Christy was saying about the collection of safety data; because I think one of the most striking things I've seen here is when an unanticipated safety event is brought to our attention, going back into the data from the clinical trials and being able to mine that data for things like kidney function, dehydration. Those kind of things, really led to critical information for unanticipated safety events. And had that data, that was collected in the clinical trial, not been as rich as it was, I don't think we would have been able to assess the later onset safety signal. I think that, again, as a member of this committee that is charged with looking at safety data, the collection and richness of that data is really critically important.

DR. PORTMAN: Kelly.

DR. WADE: Ron.

DR. PORTMAN: Yes.

DR. WADE: I think I'm hearing you. Do you have a question or a comment for Dr. Nelson?

DR. PORTMAN: I just have a comment on what you've been discussing related to the data and standardization. Both the European Pediatric Clinical Trials Network Initiative, which is under way in Europe and the IAX (phonetic) Clinical Trial Network in the U.S., which is forming now, have a major section of their operations devoted to making sure that all the studies have the unified data collection and standards. That way we can do some of the things

you have been talking about.

DR. NELSON: Thank you, Ron. And another thing, and we'll have to just double check on the methodology, but I have been involved in some workshop planning efforts where we've partnered with external folks outside of the FDA to help with the planning of that workshop. So, it occurs to me that we can figure out how best to reach out to do that. There's processes that have to be put in place, but I think they can be managed.

DR. CAMPBELL: I can certainly appreciate the desire to get devices that aren't being used out of the PAC meetings. I mean, it's always struck me that looking for safety signals with devices is challenging because they are used much less frequently than drugs and there's also user error that enters into safety signals. And I don't know that I have really a comment, but more of a sort of how can the FDA really identify devices that are dangerous to children?

DR. NELSON: I think it's fair to say that at this point we don't have criteria, per se, to say when there's no new safety concern or a safety concern. What I would certainly envision is that those reports would need to provide a justification as to whatever was observed, as to why it was, either new or not new. It would be available for review and comment. And we would have the same process by which if someone looking at that, such as yourself, or we decide to web post something and you see that and you go, oh, wait a second here. There's something here that you did not consider.

That would then come back to us in the comment period through the docket, as we're doing with the drugs, and then we would consider bringing that to the PAC at the next available meeting. That was sort of the process. But, you know, devices are a different beast and so we haven't drilled down to what that would look like in terms of when there's a safety concern or when there's not a safety concern.

DR. WADE: If I could just remind people to introduce themselves.

DR. TURER: In terms of reporting of adverse events, both for devices and for drugs, I wonder what role, if any, the FDA might play in putting that as part of education of physicians in medical school, and for even clinical pharmacists. And having a reporting process that's very easy; easy to access, easy to enter, when an adverse event is suspected. To allow that transparency. Because I think that it's something we're not taught, and when I have to do reporting of different diseases, you know, reportable diseases, it's a very laborious process.

And so, it makes it -- you know, you kind of feel like you get your hand slapped every time you do it. It's got to be easy to use, easy to do, and done professionally, I think as professionals we say this is something that's critical going forward. Is there a role for FDA in that?

DR. NELSON: Well, let me see if -- in terms of the ease -- I mean, education, certainly we can have a role in that. I guess the question is the ease of reporting. I don't know, Bob, if you have any comments on the ease of reporting, because I haven't done this in a while.

DR. LEVIN: Yeah. Bob Levin, Pharmacovigilance. This is in the early stages, but several groups in the FDA are actually developing a mobile app, which and one of the main goals is to make reporting easy and efficient. It's in a pilot stage, looking at a very specific type of event, and with certain centers. That looks promising. And I agree. We always ask ourselves to what extent people -- different healthcare professionals are aware that it's possible to report both to companies and to FDA. And we're thinking about how to improve that.

Another thing that we haven't done yet but it's in the discussion phase, is as far as motivating people to report. I know with some groups -- I don't think it's in the U.S. -- but in some regions there may be something like CME offered to clinical professionals to try to motivate people to report. But those are excellent points. You know, obviously things are vastly unreported and for numerous reasons, but one could very well be that people aren't aware of the system.

DR. NELSON: Before Bob's question let me -- it just occurred to me, maybe this is something that could be developed by the American Board of Pediatrics into an MOC module perhaps. I don't know if anybody has any influence on the board, but that might be a useful thing to think about. I'm not sure what that would look like, but adverse event safety reporting could potentially be in that context.

DR. WADE: Last question.

DR. DRACKER: Bob Dracker. I just used AVERS system last week in the electronic format which I hadn't used before. It was extremely easy to do and you can stay linked to it so they give you feedback and they keep you in contact. It was excellent. I had never -- because it was always that written form you have to fill out and send in. And this was a very nice system, I love the system. And if anything, I want to use it more. I assume that was the intent of it, but it was a great system, and I had never seen it before. I don't know when that was introduced, but it was wonderful. Do you know when it was introduced at all, the electronic version of it?

DR. LEVIN: Oh, yeah. That's been -- I mean, certain elements of that have been around for a while; but it's been more I think in the last two years roughly.

DR. DRACKER: It really was excellent though.

DR. HAUSMAN: It's been a little longer than that. It was up as sort of a beta system back when I was still in Pharmacovigilance, when I was part of the committee's activities. The other thing is, when I was in Pharmacovigilance, we put together a AERS FAERS submission 101 package. This is what FAERS is. And I believe after we discussed that at the AC, several of the members asked if they could download the slides and use them for educational reasons at whatever institutions they were affiliated with. I can't remember back how far that was, but we're certainly not averse to helping with education and adverse event reporting.

DR. LEVIN: Another element of that mobile app, I was referred to, is that it will accept more than just texts. Ideally it would include, you know, verbal reports quickly and easily and even medical record information, perhaps EKGs. We're looking at having more detail information submitted with adverse event reports.

DR. WADE: Last comment and then we'll have to move on.

DR. FISCHER: I just wanted to echo that on the device side as well, I see a lot of cultural hesitancy to report device dysfunction, particularly if it doesn't result in a major patient adverse event. I do think that there is a lot of underreporting on the device side.

DR. WADE: Well, thank you to everyone for this robust discussion. Thank you, Dr. Nelson.

OPEN PUBLIC HEARING

DR. WADE: We will now at this time open the open public hearing. Welcome to the open public hearing. Please state your name and your affiliation, if relevant to this meeting. The Food and Drug Administration believes that the agency and public benefit from a transparent process that helps insure that FDA decisions are well informed by the advice and information the FDA receives from its advisory committees.

If you have any financial interest relevant to this meeting, the FDA encourages you to state the interest as you begin. Such interests may include: a company's or group's payment of your travel or other expenses, or grant money that your organization receives from the sponsor or a competitor. If you do not have any such interests, you may wish to state that for the record. If you prefer not to address financial interests, you can still give your comments. At this point, we open the public hearing.

MR. MITCHELL: Thank you for the opportunity to speak today. My name is

Jack Mitchell and I'm Director of Health Policy at the National Center for Health Research. A research center analyzes scientific and medical data and provides objective health information to patients, providers, and policy makers. We also train patient advocates and we advocate for patients on Capitol Hill and elsewhere. NCHR does not accept funding from the drug or medical device industries, so I have no conflicts of interest to report. I am personally not an MD or clinician, but I am presenting our comments today on behalf of one of our analysts, who unfortunately could not be here today.

As you noted earlier, Congress required pediatric focus safety reviews in accordance with the Food and Drug Administration's Safety Innovation Act. This Advisory Committee meeting is an effort, a very good one, to integrate monitoring by outside experts and others to ensure that drugs have benefits which outweigh serious risks.

We are concerned about Abilify because of its well-established, serious effects of tardive dyskinesia, tremor, muscle stiffness, and sudden cardiac death. Other risks include nausea, insomnia, anxiety, weight gain, blood sugar, and high cholesterol. Moreover, the impact on a child's developing brain is unknown because we lack high quality, long-term research. The FDA approved Ability for treatment of irritability associated with autistic disorder in patients 6 to 18 years old. The drug was approved by the FDA for this indication based on two, 8-week, placebo-controlled trials.

Because the drug is intended for long-term use, but studied for only eight weeks, the FDA required a post-market study. The longer-term results indicated no significant different between Ability and placebo at week 16 in reducing the symptoms of irritability, in pediatric patients, who had already maintained a response for the first 12 weeks of Abilify treatment.

There are substantial demographic differences that raise the question about whether Abilify is less safe for girls and less effective for non-white children. Almost all the

girls taking Ability experienced adverse events, 91 percent compared to 43 percent for boys. And 50 percent of the non-white children on Ability relapsed, compared to 26 percent of the white children. Although the number of non-white children was very small, that result was still worrisome, especially since the non-white children in the placebo arm were much less likely to relapse than the non-white children on Ability, and the opposite was true for white children.

It's important to remember that all the patients who participated in the long-term study had already shown that they could tolerate Ability for at least 12 weeks. For this reason, the reviewer referred to participants in this trial as a "enriched sample", certainly not typical of all patients. Obviously, adverse events would be higher for patients that weren't selected on the basis of a previous positive response to the drug for 12 weeks.

In summary, in our view, the evidence for the effectiveness and safety of Abilify for children, with autism and symptoms of irritability, is insufficient to outweigh the risks, especially for girls and non-white children. We urge the FDA to revise the labeling to state that Abilify has not been proven effective in the long term for this indication. And I thank you for your time and the opportunity to present our perspective.

DR. WADE: Thank you for those comments. Are there any other speakers for the open hearing? We will now close the open hearing.

Our next presentation is by Dr. Carolyn Yancey.

CDER – STANDARD REVIEW OF ADVERSE EVENT - ABILIFY

DR. YANCEY: Good morning. My name is Carolyn Yancey and I'm the Medical Officer in the Division of Pediatrics and Maternal Health. And the Pediatric Focus Safety Review that I'm going to present is on aripiprazole. And to the point that Skip Nelson made earlier this morning, this is a product that's been presented to this committee two other

times.

This is the outline of what I'll be discussing this morning. I'll talk about the background of this product. That discussion will include previous Pediatric Advisory Committee (PAC) meetings. I'll also talk about the most recent PREA studies that have been completed and support new indications since it was last presented to the PAC, relevant pediatric labeling, drug use, trans adverse events, and then we'll summarize.

Aripiprazole belongs to the therapeutic category of atypical antipsychotic drugs. The dose varies by indication. The initial dose is 2 mg per day. The recommended dose is in the range of 5 to 10 mg per day. There are actually formulations that are oral products and injectable. Only the oral products are used for pediatric patients. Oral tablets, as you can see, are manufactured in six different dosages. There's an oral disintegrating tablet. There's a 10 mg and 15 mg tablet, and an oral solution, 1 mg per mL. The sponsor for Abilify is Otsuka Pharmaceutical Company.

The indications for pediatric patients appear in bold, so that's what I'll focus on. Again, only the oral formulations are used for pediatric patients. Schizophrenia is approved in adolescents 13 to 17 years of age. Acute treatment of manic or mixed episodes associated with Bipolar I Disorder. As monotherapy and as adjunct therapy to lithium or valproate, it's approved in pediatric patients 10 years to 17 years of age. Irritability associated with Autistic Disorder is approved in pediatric patients 6 to 7 years of age. And the most recent approved indication is in Tourette's Disorder, pediatric patients 6 to 18 years of age.

The original FDA approval for this formulation was November 2002. Under the Pediatric Research Equity labeling changes, schizophrenia was approved October 2007. It added an indication and affected labeling in the sections you see listed here. Clinical study is described in section 14.1. The second indication that was approved, irritability associated with Autistic Disorder. That approval was November 2009. Again, a new indication, differences in

dosage and administration specifically addressed this diagnosis and the clinical studies described in section 14.4.

The first PAC meeting, where aripiprazole was presented was December 2009. And it included new information on weight gain, which was added to labeling. There was discussion about drug use data associated with Attention Deficit Disorder without co-existing diagnoses, discussions about antipsychotic drugs used with this diagnosis, and then the update was shared with PAC.

There were PREA labeling changes in 2011, and that was for the indication of Bipolar I Disorder. And that data is presented in the clinical studies section of labeling. That was the addition. The second PAC meeting that was held, describing aripiprazole, was September 2011. And the OSC Division of Pharmacovigilance reviewed. There were no labeling changes that were recommended, and routine pharmacovigilance was recommended to be continued. PAC expressed their concerns, wanted to continue vigilant monitoring of metabolic syndrome; metabolic syndrome in this case, hypoglycemia, diabetes, dyslipidemias, and of course the weight gain.

The PREA labeling changes that next occurred were June 2014, irritability associated with Autistic Disorder. That affected dosage and administration section of labeling and clinical studies. Within that same year, December 2014, Tourette's disorder was added with a pediatric indication. Again, comments in indications, dosage and administration, pediatric use, and clinical studies.

Over the next four slides I'll address the two most recent indications that have not been presented to PAC before. The first, irritability associated with autistic disorder. There were two 8-week efficacy safety studies in patients 6 to 7 years of age diagnosed with irritability associated with Autistic Disorder and behaviors such as tantrums, aggression, self-injurious behaviors, and a combination of these. There was one 12-week randomized

withdrawal maintenance of efficacy study in the same pediatric patient population. The efficacy endpoints are as you see them presented, irritability subscale of Aberrant Behavior Checklist, and that's the acronym, ABC-I, and Clinical Global Impression-Improvement scale.

The outcomes of these studies are as follow. The efficacy results in the 8-week study, study 1 had a total of 98 pediatric patients. Those were the doses of aripiprazole that were evaluated. Outcomes showed significantly improved scores for the Aberrant Behavior Checklist subscale as well as the Clinical Global Impression-Improvement scale compared to placebo. And that was across the three doses that you see in parenthesis.

For study 2, there were a total of 218 pediatric patients. This study looked at three fixed doses of aripiprazole compared to placebo. Again, outcome significantly improved scores on irritability based on both of those primary efficacy endpoints. There was a 12-week, randomized, withdrawal study in 85 patients, 6 to 17 years of age, again, same diagnosis. And this study failed to establish long-term maintenance.

Tourette's Disorder is the most recent indication for this formulation that occurred December 2014. There were two studies, an 8-week placebo controlled fixed dose trial. Pediatric patients were 7 to 17 years of age. And there was a 10-week placebo controlled flexible dose trial, 6 years old to 18 years of age in patients with Tourette's Disorder. The primary efficacy endpoints across these two studies with a Total Tic Score and the Yale Global Tic Severity Scale as well as the Clinical Global Impressions Scale for Tourette's Syndrome.

The efficacy results showed the first study, which included 133 pediatric patients using aripiprazole. It was a low dose and a high dose and this is weight based. The high dose, and the low dose groups, demonstrated statistically-significant improved scores on both of those primary efficacy endpoints. Study 2 had a total of 61 patients and aripiprazole was evaluated over a range of doses, 2 mg to 20 mg per day. Again, it demonstrated statistically-significantly improved scores across the latter primary efficacy endpoint.

Over the next six slides I'm going to describe to you labeling that addresses pediatric information. The box warning, we know it well. It includes increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. It certainly underscores the need to monitor for worsening and emergence of suicidal thoughts and behavior.

Section 2, and I've just listed in bold those sections that apply to the pediatric indications. Section 2.4 addresses dosing recommendations for irritability associated with Autistic Disorder. Section 2.5 addresses Tourette's Disorder.

Section 5, warnings and precautions. Section 5 is quite lengthy and for certainly justifiable reasons with this formulation. Section 5.3 addresses suicidal thoughts and behaviors in children, adolescents, and young adults. And, of course, this certainly supports what's in the boxed warning. 5.4, Neuroleptic Malignant Syndrome, 5.5, tardive dyskinesia, 5.6 metabolic changes, hyperglycemia, diabetes mellitus, dyslipidemia, and the weight gain has certainly been addressed in the past. Section 5.7, compulsive behaviors, 5.8, orthostatic hypotension.

5.9, falls. 5.10, leukopenia, neutropenia, agranulocytosis. 5.11, seizures, convulsions. 5.12, inability to certainly process certain cognitive and motor impairment issues. Body temperature, section 5.3. Disruption of the body's ability to reduce core body temperature; and I'll speak to this in a few additional slides. And, of course, 5.14 is suicide.

In section 6.1, clinical trials experience, addressing commonly observed adverse reactions. If you look at the third bullet point, irritability associated with autistic disorder. Reported events were sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder events, and lethargy. For Tourette's, again, sedation, somnolence, nausea, headache, nasopharyngitis, and fatigue.

In subsection 14.4, the clinical study's data is presented for irritability associated

with autistic disorder, and both clinical studies are described in that section. Section 14.5 includes Tourette's Disorder again. Those two studies in that disorder are included.

This is our most recent information on pediatric drug utilization. The grand total, as you can see -- it includes adult patients as well as pediatric patients -- is over two million. If you focus on those middle rose, 0 to 17 years of age, we have a total of 517,403 patients. And if you look at the age breakdown, the majority of the children fall within the approved age ranges that appear in labeling, 6 years to 17 years of age.

The pediatric diagnoses, if we look at ICD-10 codes, in the age group 6 to 12 years are the most common ICD-9 diagnosis that was apparent was infantile autism. And in the 13-year to 17-year age group, affected psychoses was the ICD-9 code that was most often reported. No drug use mentions or associated diagnoses were captured for 0 to 5, appropriately so.

In the FDA Adverse Event Reporting System (FAERS) that you've heard much about yesterday as well as today, the data presented is from May 1, 2011, to November 30, 2016. And I want you to focus on those two middle rows, pediatric patients 0 to 17 years of age. If you look at the serious reports in the middle column, domestic U.S., we had a total of 515 with 32 deaths. And then in that third row, 17-year-olds, 17 to less than 18, there were a total of 66 domestic reports and 5 deaths.

On this slide the top box, as well as the box to your left, are talking about crude cases. I just want to clarify that before I start to talk about the numbers. So, the serious pediatric reports crude count, 581 patients. If you look to the box to the left, the excluded cases, and I won't go through that list, but it gives you an idea the kind of duplications that our OSE group takes care of and removed from the total number of crude counts. We're going to focus the rest of this presentation on the numbers you see presented in the small right-hand box, pediatric case series. There was a total of 78 cases and it includes 14 deaths.

Just a 30,000-foot view of the characteristics of those pediatric case series with oral aripiprazole. There were 46 males, 31 females, and 1 case where it was not identified. On the ages, this gives you a typical breakdown for use of this product. Majority of the patients are between 6 years of age and 17 years of age.

There were serious outcomes. Death, there were 14 deaths as I mentioned. And I will go into more detail in those, in a few slides, but this is just to give you an overview of the serious events that have been reported. There was one case of transplacental exposure, a premature infant that died at six days of age. The remaining 13 cases were children, adolescents, between 5 and 17 years of age. The reported daily dose ranged from 3 mg as high as 30 mg per day. And that was reported in a total of six of these 14 cases. Also, two of three cases reported toxicity to several concurrent medications, intentional overdose, resulting in a completed suicide. And one of these three cases did not explicitly report intent to self-harm. We'll talk about that in a moment. The other numbers you see are simply a demonstration of the other serious cases, life threatening. And 19 of these 78 cases were hospitalized. A congenital anomaly was involved in one. Other serious events were a total of 56.

On the next slide, the pediatric deaths, total of 14, again. And this is the breakdown of the diagnoses for those demises. There were four suicides. There were two drug overdose. Neuroleptic Malignant Syndrome was reported in one pediatric patient. Metabolic changes in one as well as seizures, convulsions in one. Hyperthermia, this is underlined because hyperthermia does not appear in labeling. And this involved one case, so this is an unlabeled event. Cardiac, one case, unknown, two cases, and not applicable was one. If you look across these 14 deaths, there was no discernible pattern for the reported unlabeled events. And keep in mind temperature regulation and Neuroleptic Malignant Syndrome are now labeled events.

In the subsequent slides I'm going to go through brief narratives about each death.

There were four suicides, a 16-year old female, diagnosis of depression, adjunct treatment with escitalopram. I may not be pronouncing that correctly. This patient died of suicide by hanging. She was taking escitalopram 20 mg a day and experiencing mood instability. The dose of aripiprazole was 2.5 mg per day, and it had been started as adjunct therapy for three months. This teenager was described as continuing to have rage outbursts. The dose was increased, actually to 5mg per day for three weeks, and there had been no prior history of suicide attempts in this adolescent female.

There was another 16-year old female, diagnosed with major depressive disorder with atypical features, and she died of suicide, we don't know the method. There was a 16-year old male. Diagnosis for the aripiprazole treatment was not reported, and he died of cardiac and/or respiratory arrest. And this was secondary to intentional drug overdose. There was also an acute ingestion of morphine sulfate, acetaminophen, hydrocodone. And lastly, a 17-year old male diagnosed with bipolar disorder, treated with aripiprazole for about six months. Died from a self-inflicted gunshot wound. We did not have additional details.

There were two drug overdose cases. A 14-year old male. We don't have the underlying diagnosis, reason for aripiprazole treatment. Died of cardiac and/or respiratory arrest secondary to drug poisoning. Died post drug poisoning, and there's quite a list of medications as you can see. Suicide intent for this case was not reported. The second overdose case is a 17-year old female, Bipolar Disorder. Died of hypoxic encephalopathy due to acute bupropion and aripiprazole, but only bupropion was reported in the serology tests. And the death was attributed to the bupropion.

Neuroleptic Malignant Syndrome was reported in one pediatric patient. It was a 12-year old boy. Underlying diagnosis, bipolar disorder. Died of possible neuroleptic malignant syndrome. The dosage for aripiprazole was 10 mg per day. Metabolic changes occurred in one patient, in a 14-year old male. The correct narrative for this is not the one you

see on the slide. The correct narrative for this was cardiac arrest, Hyperglycemic, Hyperosmolar, Nonketotic Syndrome.

The last case on this slide, seizures and convulsions, reported in one patient, a 5-year-old boy. Underlying diagnosis reported was simply behavior disorder. Died of sudden unexpected death with epilepsy. Concurrent medications, carbamazepine and levetiracetam, aripiprazole 3 mg per day.

There was one case of hyperthermia. This was in an 11-year old male diagnosed with bipolar disorder. He died while playing outside. There's no cause of death reported. Prescribed several other medications, drugs. These were not reported. The internal body temperature was reported as 106 degrees. The dose of aripiprazole was 30 mg per day.

There was one case, a 10-year old male reported as a cardiac death. We don't have the underlying diagnosis, reason for the treatment. In terms of the reason, causality for death, he died of multiple organ failure, ischemic cardiomyopathy, coronary artery stenosis, congenital heart disease, and the aripiprazole treatment had been going on for two years. We don't have dosages for this case.

We have two cases that are unknown at this point. A 13-year old girl, underlying diagnosis of bipolar disorder, treated in combination with valproate. She died secondary to drowning in a pool after saying she was tired. The aripiprazole dose was 10 mg per day and in a prior week she had been prescribed a cough medication. A 16-year old male, underlying diagnosis of Autism, cause of death not reported. Died while taking aripiprazole for three months duration. We don't have any information for the dose for that child.

There is one case that's listed as not applicable. And this, again, is the 5-day old infant male, transplacental exposure to aripiprazole. Died of complications related to congenital anomaly Tetralogy of Fallot, included post-op hemothorax and hemopericardium. The maternal history had chromosomal abnormalities, so there was no causality related to the aripiprazole.

The next two slides, I'll address the non-fatal serious pediatric adverse events. There was a total of 64. Stay with me as I describe this first bullet. There was worsening of underlying condition after switching from brand to generic drug in 16 patients, from one dosage formulation to another dosage formulation in three patients, or from a generic to a brand in one patient. The condition did not improve in 11 patients or either worsened in four during aripiprazole treatment. There were five cases of reported cerebrovascular infarctions, cerebrovascular accident. The subsequent diagnosis that you see are underlined because they currently do not appear in labeling, but they were reported as gynecomastia in three patients, hallucinations in three, pancreatitis, pancreatitis disorder, two, non-alcoholic steatohepatitis in two, and drug screen false positive for amphetamines in two. Keep in mind aripiprazole is labeled for delirium.

There was one event for each of these. I won't read through the list. But the message that we share with you on this slide is there's no discernible pattern for previously unlabeled events.

In conclusion, this completes our presentation about aripiprazole focused pediatric safety review. Our conclusion is there are no new safety signals identified. The agency recommends continuing ongoing post-marketing safety monitoring. And again, we pose the question to you, does the committee agree?

DR. WADE: This discussion is now open for questions. Please introduce yourself.

MS. CELENTO: Yes, Amy Celento, patient representative. In terms of the prescriptions for irritability associated with Autistic Disorder, it looks like about 24 percent of the patients based on the prescription data provided here, so about 700,000 kids are getting aripiprazole for irritability associated with Autistic Disorder. I have some concerns because

about 25 percent of kids, with ASD, are considered non-verbal. I'm not really sure how anybody would assess what's happening for those children on this medication.

Akathisia is not reported under this category. However, I'm not sure if autistic kids, verbal or nonverbal, would be able to convey if they're having suicidal thoughts or if they feel like they want to jump out of their skin. I have some real concerns about this medication showing, potentially, a lack of efficacy in this category, you know, based on the data we see here, and to the point made in the open public forum. I'm concerned that this medication prescribed to these children could be causing extraordinary stress, you know, a significant amount of undue stress and uncommunicated impact, when prescribed for irritability associated with Autistic Disorder.

DR. MCGOUGH: This is Jim McGough, Dr. McGough, and I'm actually the second author on the risperidone irritability study, so I'm very familiar with this. The main outcome measure, the ABC irritability scale, is based on observations by the parent in terms of things like aggressive outburst, et cetera, et cetera. So that's how irritability is defined. It doesn't rely on the child saying, "I'm really feeling irritable." What it refers to is over reactivity to stimuli that manifests in terms of outbursts and tantrums. The verbal abilities or nonverbal abilities really isn't a factor.

In terms of the -- we have to be careful with the maintenance study, which, again, they're not saying it didn't work. They're saying it failed to show a response. Now, interesting, in the risperidone study, when we blindly withdrew people, the relapse was so profound we actually stopped the study early, because it was so significant that it would have been unethical to continue. It's interesting that this didn't happen here, but we're only talking about 85 kids. You know, an initial thought would be that just it's not powered really to show a difference. The fact that it didn't prove efficacy doesn't mean it wasn't working.

MS. CELENTO: Thank you for that. I do understand that the assessment of

irritability, that the scale is based on observation. What I'm saying, is that I'm not really clear if these children can communicate if the medication is causing them additional stress; if they are feeling things like they want to jump out of their skin or having suicidal thoughts. That's what I'm saying. I have concerns about that. I appreciate what you're saying, and in terms of the risperidone study and having to stop withdrawal, again, a small population of 85 kids. I just wanted to express my concerns about this. Thank you.

DR. HAVENS: Are we asked to comment on the studies that were in the background in terms of efficacy? Is that part of what we should be looking at here?

DR. HAUSMAN: Yeah. Hi, this is Ethan Hausman form DPMH. There is some variability in how the presentations are given to the advisory committee. The Pharmacovigilance people do the report. The pediatric material health clinical reviewer thought that providing some information on the studies, that were actually performed, might help provide some background when you look at the safety. But the charge of the committee today is to look at the -- the main charge is to look at the post-marketing pharmacovigilance data.

The pre-market study information was just provided for your background. The charged committee is not to comment, per se, on the effectiveness of the drugs as demonstrated in those studies.

DR. HOEHN: I wasn't sure Dr. Havens was done. I had one comment and one question. My one comments is it looks like a few more of those deaths could probably be categorized as self-harm, because there were four suicides, two drug overdoses, and then it seems like the metabolic changes one was also a drug overdose. I just wanted to point out, I wonder if we're underreporting suicide just based on the lack of details. It seems more like seven of them were that.

And then my question was related to the hyperthermia, whether it was spontaneous hyperthermia, or if there was any information available if it happened on like 110-

degree day, if there were environmental factors or other things that contributed to the 11-year old hyperthermia.

DR. HAUSMAN: I'll defer in the name to the Pharmacovigilance reviewers, but one apparent disconnect between our presentation and the pharmacovigilance review, is that because there was a question about suicidal intent with one of the overdose cases that we listed as two, that came into Pharmacovigilance as a reported suicide. However, the report also stated that suicidal intent was not provided or not commented upon. For the patient, I believe you were referring to with the hyperglycemic hyperosmolar coma, the hyperthermia?

DR. HOEHN: There was one metabolic one that was attributed to hyperosmolar --

DR. HAUSMAN: Yes.

DR. HOEHN: -- hyperglycemia metabolic one, that in the report it says there were multiple drugs and it was all secondary to drug poisoning. I'm just saying that one doesn't seem like it was acutely related to just that. It looks like that one could have been self-harm. But it was the other one on the next page, where they talked about the 11-year-old found down with a temperature of 106. That was the one that I was inquiring about what we knew about the environmental temperature. That's a different one.

DR. NEVO: Hi, this is Noah Nevo from Pharmacovigilance. In regards to the metabolic change, that one was actually, the case narrative on the slides was not correct. So, the patient wasn't exposed to all of those medications. And in the case, the parents actually denied a drug overdose for that specific patient. In regards to the hyperthermia case, there was really limited information in that case. It basically was saying that the child was playing outside, or doing yard work, and just dropped dead. So there really wasn't any additional information about what was going on there.

DR. HOEHN: Sorry. I have a follow up question to that. Do you know what

month or what state? I mean, it seems like you could extrapolate some if you knew it was summer or winter and if you knew it was Florida or Maine.

DR. NEVO: Let's see here. It doesn't say the date the event happened. It was reported in May of that year, but that doesn't necessarily mean that that was when the event occurred. And I do not have information about the geography of the event.

DR. WADE: Okay. I have taken note of the hands. We'll start with Dr. Jones.

DR. JONES: Bridgette Jones. I was just wondering if the sponsor has followed up on the relapse rate, the different in relapse rate between non-white and white children. It was included in our background information, and it looks like relapse rates were about 50 percent higher in non-white children. I don't know if there has been any follow up on that.

DR. LEVIN: Are you referring to the control trial, the maintenance study?

DR. JONES: Yes. Uh-huh.

DR. LEVIN: Yeah, we could find that out. We don't' have the information here, but we could look into the review and provide the information. There is often limited information, but we could probably provide numbers at some point.

DR. JONES: Okay. Yeah. This is the post-marketing trial where the outcome was relapse rate, and they saw differences between white and non-white children in that outcome. It was like Table 9.

DR. HAUSMAN: We have a representative from the Division at the end of the table.

DR. MARC STONE: Yeah. That's certainly a question we can ask the sponsor. I think the -- of course, the evidence from the trial, because of the small numbers involved, is pretty negligible. It would be difficult, although I think there may be some ability to recognize this, to -- outside of a controlled trial, to recognize differences in relapse rates because of all the other variables involved; who was observing, how they're being observed, those sorts of things.

But I think that's a legitimate question and I will look into pursuing it.

DR. JONES: Thank you. Yes. I realize the numbers are small, in general for the trial, and I think that sometimes these safety signals are observed in underrepresented groups; and it's hard to figure out are those really actual real trends we're seeing or not. I think those are definitely worth following up and I thank you for that.

DR. WADE: Okay. We'll go to Dr. Callahan followed by McGough and Turer.

DR. CALLAHAN: I guess my concern is when you look at section 6.1, clinical and trials experience and other reports of these adverse events; that they don't get properly classified, which then minimizes certain adverse events. For example, they list salivary, hypersecretion, and drooling, which are probably most likely extrapyramidal disorders, and they're not being counted as such. I think the result is you undercount things like extrapyramidal disorder.

And the other thing that's striking, in the clinical trials experience, is for whatever reason, probably by the design of the trials, they did not even capture weight gain and increased appetite. In fact, they list decreased appetite. And I think those of us who do prescribe these drugs know that increased appetite and weight gain is to be expected. And, again, it's not even identified. I think we need to figure out a way to capture these adverse events and identify them in the trials, as well as in the post-marketing experiences, better.

DR. LEVIN: On the point of metabolic abnormalities, yeah, it looks like it's not itemized by study. But in the warning for metabolic effects, I think they -- after the study it looks like the sponsor combined, did an aggregate analysis in pediatric patients. But I agree with your point, that it's not specified for this trial. But there's a lot of information in the warning section about metabolic abnormalities.

DR. CALLAHAN: But again, I think when you state it simply as metabolic abnormalities, I think to many who read it, they don't consider weight gain when you just

mention metabolic abnormality. I think it's kind of, again, broad and vague and doesn't specify which metabolic abnormalities are we referring to.

DR. LEVIN: Yeah, let me check that. I think it does. Typically, we do describe weight gain in the metabolic abnormality section, in Section 5, but I'll check that right now.

DR. HAVENS: Weight gain is in the label.

DR. CALLAHAN: Right. I know it's in the label. But my concern is if the sponsors don't identify it in their clinical trials, my concern is they're not really looking for it, and that the trials aren't designed to identify some of these common side effects.

DR. LEVIN: Yeah. I mean, those are typically -- I know in psychiatric trials, it's a standard assessment we require. It may not be reflected in the label in detail, but those are elements that are looked at fairly routinely. So, it may be a function of not specifying the findings by study, or indication, that there's a lumping of the pediatric data.

DR. HAUSMAN: Does that address the point, you think?

DR. CALLAHAN: No, no, I don't think so. I think, you know, this medication and then commonly stimulants, they just don't identify these side effects. Like most kids have appetite loss with stimulants. If you look at the FDA labels, the incidents of loss of appetite and weight loss is very small, just like in this label the incidence of weight gain is very small. And so, I don't think the sponsors design the trials to correctly identify these side effects, and so they are underestimated and listed as small, when really they are usually quite great. I think that's something that we need to look at with trial designs and how they report adverse events and side effects, and how they look at things like weight.

DR. LEVIN: Yeah. Actually, that reminds me of another important point. Tell me if you think you agree with this. I think that typically, the acute, controlled trials are relatively short, so it often does not pick up the more chronic effects of weight gain. We try to reflect that it may vary by study and by drug, but we understand your point. It's obviously a

major side effect, and it is quite common with chronic use.

DR. MARC STONE: If I could comment on that. I'm the Deputy Director for Safety for Psychiatry. And I think the point that Bob made is true, weight gain, when it's defined as an adverse event, it's stated as a standard of like a 10 percent gain in weight; which is unlikely to happen in a short time period, even if the drug tends to cause weight gain, so you're not going to see them crossing that threshold.

What you may see is, you know, weight is also treated as a vital sign. Children's weights are recorded throughout. You could see the average weight in the study increasing relative to placebo, which would tend to confirm what we know about these drugs; but it won't be listed as an adverse event.

And so, we say it's consistent in what we're seeing. But I do think when we -- and this is something that I've been emphasizing, is that we shouldn't look at adverse events just as thresholds, but if we look at the tendencies within clinical trials, even if they don't lead to discreet obvious adverse events, that they point to potential safety issues with the drug. Well, weight gain is well known with atypical antipsychotic, so nobody would be particularly surprised if they saw an average weight gain relative to placebo in the study. And, you know, weight gain is in the label. But in terms of picking it out at individual trials, I think you run into that issue.

DR. WADE: We're going to continue this discussion. I've got McGough, Turer, Neville, and Havens. Dr. McGough.

DR. MCGOUGH: Looking at the adverse events, particularly serious adverse events, investigators in IRBs, of course, make a determination about likely related, you know, probably related, not related. Is there any implicit assertion by listing the -- I mean, it seems to me that you're just reporting what was reported to you. Is there any implicit sense that these are due to the drug, or is this just a neutral, this is the report we received? Because for almost all of

those deaths, I would see alternative explanations.

The person with the sudden seizure was on two seizure medicines, et cetera. The person with no suicidal intent appeared to have taken everything in his medicine cabinet. People with bipolar disorder kill themselves. Again, is it implied this is due to the drug, or is this simply a report of what was observed in people who were on the drug?

DR. NEVO: Yeah. That's a great question. The death cases, we made the decision to report -- include in our review -- all death cases regardless of whether they had any causal relationship with the drug. And we agree with you that in most of those cases there was no direct association with aripiprazole in those death cases.

Regarding the other non-fatal serious reports that we included and listed, if the case was completely unassessible, we excluded it from the case series. If we could not make any connection between the adverse event, and the drug, we excluded it. If there was an alternative ideology, we also excluded it from the case series. All the non-fatal serious cases, we included in the case series, could have anywhere from an unlikely to possible causal relationship with the drug.

DR. WADE: Dr. Turer.

DR. TURER: Christy Turer. As a follow up, regarding the comment about weight gain, I think it's insufficient that we just state that weight gain is a problem. I think it needs to objectively measured. I think it needs to be indexed via Z scores. It's not currently. Many of these trials, they have parents report weight gain. They don't objectively use the weight and height data. That is problematic.

As a provider, I want to know what is the incidence of weight gain? What is the amount of weight gain, per dose of drug, that I can expect? Can I compare the impact of this drug versus another one? All of that information is critical, not just is there weight gain or not. That's point number one. The public speaker yesterday clearly stated parents don't recognize

their kids gaining weight, so parental report, we have data. It's not accurate. I think it's incredibly important that we objectively measure this.

Number two, my concern is, ischemic cardiomyopathy, coronary artery stenosis, cerebrovascular accident, these are not labeled events. But these were seen in patients taking this drug two years or more. Those are adult diseases, that we're increasingly seeing at earlier ages. And so, you know, it's notable that for weight loss drugs to gain FDA approval, we have to do protracted cardiovascular disease outcome studies. But we're doing 8-week trials on drugs we know cause metabolic problems, approving them. I would argue these are new safety events. This is incredibly concerning to me. I understand the child had underlying congenital heart disease, but congenital heart disease, at ten years old, does not cause coronary artery stenosis or ischemic cardiomyopathy. That, to me, was like, really?

I would want to better understand that. With the cerebrovascular accident, follow up questions I'd want to know is, were those females -- were they on contraceptives? I think those things really bear sorting out.

DR. HAUSMAN: Hi. This is Ethan Hausman. I agree with everything you said. I would mention that the ten-year-old, who did have the ischemic cardiomyopathy and stenosis, also had a congenital heart disease documented. DPV does a heroic job doing the best they can, sometimes, with somewhat limited data. And it's a joint effort when we put the presentations together, of course.

We're not blind to looking at the reports and we do the best with the information that we have. And one of the things that can help us moving forward is, as an outgrowth of the work of the committee, that it's filtering out into the community that the better the data in the report that comes into FAERS, the better assessment that the people who report those incidents give to us, the better we can assess those cases. So, we agree with you.

DR. WADE: Dr. Neville.

DR. NEVILLE: Hi, Kathleen Neville. I wanted to follow up on the previous question because I saw the CVAs and strokes, and I'm concerned about that. I'm wondering if we understand the underlying ideology. I mean, that's 8 percent of that patient population, and to me that would be a potential signal.

DR. NEVO: In regards to those five CVA cases, four or the five cases reported very, very limited clinical details. I don't have any information on concomitant medications or past medical history, so really difficult to assess what was going on, whether it was even really a CVA. That was just a reported adverse event, but no clinical information to help assess what was actually going on in the case.

In the fifth case, they did report some additional details, which I can share with you. It says that the patient was admitted for stroke-like symptoms. That included a complete loss of feeling on her left side. And she felt freezing cold and had a dilated eye pupil. And the report did include information about clinical workup, but didn't report the information from that. And the review is available online, with the material for this meeting, so that information is available to the public. But this patient was actually treated with medications that were more consistent with treatment for a migraine headache, and there was never actually confirmation of a CVA in that case.

My conclusion was we couldn't really say that it was actually a CVA, even though that was what was reported. But there was no objective information provided to confirm that that was the diagnosis. And the treatment provided wasn't consistent with treatment for a CVA.

DR. NEVILLE: Can I just follow up with a question to that then? We're calling them CVAs because people are telling us without good data?

DR. NEVO: That is correct, yes.

DR. NEVILLE: Okay.

DR. LEVIN: No, it's a very common problem with post-marketing adverse

evented reports. And I would guess mostly likely that was -- well, I'm not sure if it was reported by a clinician or reported by a patient or family. Yeah. I don't think we had that information because we were looking at those cases too.

As far as the question of mechanism, it's a great question. In numerous antipsychotics, even a warning, a class warning for CVA, for antipsychotics, especially in adults. And I think it's safe to say we don't know the mechanism. One theory, of course is, is it general thromboembolic effect. And there's been numerous epidemiological studies with varying results, and we had to examined that in great detail and it's hard to even -- there's definitely an association between antipsychotics and thromboembolic events. Whether it's a causal connection, there's a lot of debate about that and uncertainty.

DR. NEVILLE: I understand that, but thromboembolic events in adults are quite different than children, and that's where my concern comes in.

DR. LEVIN: Right. Yeah. I think it's a great question. I don't think we have answers for that. The other thing is that a lot of these antipsychotics, the atypicals almost all have significant serotonergic effects which could affect platelet function; that's another theory about possible mechanisms, the connection between these drugs and the CVAs or other embolic events.

DR. NEVILLE: Then does it warrant further examination? I mean, we're doing safety monitoring, I understand that. And I understand the limitations that you're under. The data are only as good as -- trust me, I read hundreds of safety reports from adult studies, and the data are only as good as what you get. But I'm still, as a reviewer, left with 5 out of 64 kids being reported to have a CVA, which to me is significant.

DR. LEVIN: Right. There are a number of things we can pursue including potentially datamining. I'm not sure if we -- we may have done that.

DR. NEVO: We do keep an eye on all adverse events on an ongoing basis, so we

are continually monitoring for these adverse events. And I also just wanted to clarify that that case where it was a CVA, but probably wasn't really a CVA, was reported by the patient's mother; and she reported stroke-like symptoms, and so that's how it got coded was CVA.

DR. WADE: Dr. Nelson.

DR. NELSON: Let me just ask a quick question of our OSC colleagues. How many adverse events, total, come in per month to the agency out of curiosity? Just give me a ballpark number, and then I have a comment to make.

DR. LEVIN: I think in the past year it was 1.8 million, so it's a huge number.

DR. NELSON: All right. I sometimes wondered, having been on both sides of the fence; years ago, in the 1990s I remember, in a neonate who was diagnosed with CF, starting pancreatic enzyme replacement and that infant developed an intestinal stricture. And I get a phone call from FDA. And I wondered why in the world -- gee, I got a phone call from FDA. And I didn't quite understand that; and I didn't quite understand why that wasn't done all the time.

Well, 1.8 million, that's why it's not done all the time. Recently I was consulted on a newer pancreatic enzyme replacement product, and so I reviewed the history of the products and discovered that -- since I now have access to the internal documents -- that at the very time I reported that adverse event, out of Children's Hospital in Wisconsin, there was a track safety initiative going on within the FDA. And so, as soon as the call came in they go, oh, another case, and they called. Now that just doesn't happen routinely. It would be impossible to follow up.

And so, it goes a little bit back to the comment about education. Garbage in, garbage out. I mean, if people aren't providing the kind of clinical detail necessary to make the sorts of judgments you all are talking about, FDA is sort of looking at it and thinking, okay, what can we make of this? And it's not easy. And so that's part of the problem and part of, in

my mind, the challenge of asking what's the best way to do pediatric pharmacovigilance. This is a passive reporting system. It's impossible for FDA to go out and get the clinical detail unless it happens to hit at a moment, where it's looking at a specific adverse event, and doing a specific inquiry. That's part of the challenge here.

DR. WADE: Dr. Neville, sorry.

DR. NEVILLE: Don't misunderstand me, it's not a criticism. It's just when you're sitting here and you look and see five CVAs, you know, and with drugs that likely caused them in adults, for reasons that would be unique to children, it's concerning. Please don't misunderstand me, I get it; because I read the hundreds of garbage safety reports that adult PIs submit, so.

DR. LEVIN: No. Yeah, we agree it's obviously very concerning. There's at least three things we could do. One is we could -- we may have done some of these. We could follow up. Actually, as long as there's contact information with reporters, we can follow up and see whether there's additional information. That may have already been done. And we can ask companies to do that.

Secondly, we can do datamining, which specifically, for us, means disproportionality analysis. We could compare CVAs and similar events among drugs, within the class of antipsychotics and with the whole drug world in general. And we could also consider asking the sponsor to look at both their post-marketing and pre-marketing database regarding these. So, there's things we can do to pursue that.

DR. NEVILLE: Thank you.

DR. WADE: I'm hoping we can try to wrap this up for a vote. We're running about 30 minutes behind. Dr. Turer.

DR. TURER: I was just going to state if we have a really well put together monitoring system it could even be graded with, you know, are these parental reports, are they

backed up by, you know, physician reports? Do the physician reports include not just historical information, but also lab information, study information to really back that up?

The concern is there has actually been an eightfold increased risk in stroke in young adults. There has been a twofold, 50 percent increase in heart failure incidents in 20 to 35-year-olds. We have our first 7-year-old that had developed hepatocellular carcinoma from fatty liver. So, these are real concerns, and I think the understanding of physicians could be improved by better monitoring systems where we can pick these things up.

DR. WADE: Dr. Sayej.

DR. SAYEJ: Thank you. I just would like to point out a couple of things. I echo Dr. McGough's earlier comment that it's really difficult to pinpoint what the exact trigger or cause of these adverse events, or the serious adverse events, or even the death in these patients. Additionally, kids are not little adults, however, we can certainly learn a lot from the available adult data. And I do understand that, you know, adverse events are not very well reported, both in the adult and pediatric population. However, we do have a significant number of reported events on this drug at least.

Looking at the data on slides 17 and 19, and trying to just make sense of some of the data and where the frequency of adverse events and deaths that have been reported, in regards to the overall utilization in both the adults and pediatrics. It looks to me as if the adverse events and the frequency of deaths in the pediatric population was actually a lot less than the adult population. So, if we look at the number of adverse events in relationship to the drug utilization in pediatrics, you only have about .38 percent of adverse events, compared to .48 percent in the adult population. The number of deaths if .007 percent in pediatrics versus .032 percent in the adult population, which is almost four and a half-fold less common in pediatrics. While I seriously have concerns about these events, but they would have to keep in mind that they are reported a lot less frequently than we're seeing in the adult population, which

raises red flags as to what's going on in the adult population.

And I wonder what those adverse events or the causes of death in the adult population, compared to the pediatric ones, if there is a significant similarity in terms of the coronary stenosis and the hyperthermia and metabolic disturbances; then we have something to talk about a little bit more. But if they're completely isolated, and not related to any of the adult events, then it could certainly be something of a freak accident or some freak events. The chances of dying, in general, in drug overdose is 1 in 96. And chances of dying from being hit in a car is 1 in 645. And the chances in this population is 1 in 263. So that's of concern, of course. But I don't see it as being a big problem in the cases reported in pediatrics as it is reported in the adult population.

DR. WADE: Great. While we deal with, I think, the last comment from Dr. Cunningham I'm hoping that the audio-visual people could put up that slide on the vote. Dr. Cunningham, do you have a comment?

DR. CUNNINGHAM: Just we're mandated to do opioid CME training. As I hear all this information about not getting the right information that's really important, I just wonder if we might put in the back of our heads how we might mandate people having safety reporting, CME.

DR. WADE: I second that comment. And whether or not that's an FDA education initiative or an AAP education initiative, we certainly need education in this domain.

DR. NELSON: I don't think the FDA can mandate CME under any circumstances, unless there's a Risk Evaluation and Mitigation Strategy (REMS) in place and we do physician prescriber like opioids; and even there it's a problem, so.

DR. NEVILLE: And neither can AAP, but AAP can work with FDA to develop a curriculum.

COMMITTEE VOTE - ABILIFY

DR. WADE: I believe we can get the slide up for the recommendation for aripiprazole focused pediatric safety review. On this slide, as you see, the pediatric safety review, from the FDA, was that no new safety signals were identified and the FDA recommends to continue ongoing post-marketing safety monitoring. Does the Pediatric Advisory Committee concur with the continued ongoing post-marketing safety? Voting is now open.

DR. WADE: So the vote is here as you can see. There are 12 votes yes, 0 abstain, and 2 contraries. If we can go around the room starting at our left with Dr. Campbell and affirm your vote.

DR. CAMPBELL: This is Jeff Campbell. I concur.

DR. SAYEJ: This is Wael Sayej. I concur.

DR. TURER: This is Christy Turer. I voted no. I'd like to see increased vigilance and focused review of some signals that I think are new.

DR. FISCHER: Gwen Fischer. I concur.

DR. HAVENS: Peter Havens. I concur, but I hope that the results of the negative long-term study might be included in the label.

DR. CUNNINGHAM: Melody Cunningham. I concur.

DR. CATALETTO: Mary Cataletto. I also voted no. I would like to see a more focused and a shorter time period to the next review.

MS. CELENTO: Amy Celento. I concur, but I also would like to see the results of the long-term study and the label.

DR. WHITE: Michael White. I agree.

DR. NEVILLE: Kathleen Neville. I concur and I feel satisfied about the increased scrutiny about the cerebrovascular events.

DR. CALLAHAN: David Callahan. I concur.

DR. MCGOUGH: Jim McGough. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. HOEHN: Sarah Hoehn. I concur.

DR. WADE: I'd like to thank the PAC for this robust discussion and information on the safety review. I think at this point we will take a short break. And perhaps we can come back from break just a little bit early to try to continue and get back on schedule. We will continue with a discussion, when we return, on Keppra or levetiracetam extended release.

[BREAK]

CDER – STANDARD REVIEW OF ADVERSE EVENT - KEPPRA

DR. WADE: Great. We're going to get started again. Just a reminder, we have a plan for how we're going to catch up today. We're going to have Dr. Mulugeta speak about Levetiracetam, and then we're going to quickly go through the device reviews in a quick, expedient fashion. And we're going to conclude with the Kidnet Trajectory which, personally, I thought was a really exciting project. And we'd like robust discussing for Dr. McMahon's presentation.

So, moving right along. We're going to have Dr. Mulugeta give us a safety review update on levetiracetam.

DR. MULUGETA: Hello. Lily Mulugeta. I'm a clinical reviewer in the Division of Pediatric and Maternal Health. And I'll be presenting the Pediatric Focused Safety Review for Levetiracetam or Keppra. This is the outline of my talk, and in the interest of time, I won't go through all the bullets.

Keppra was originally approved in 1999. And as we all know, it's an antiepileptic. It has multiple formulation and routes of administrations that are FDA approved.

There is an oral immediate release tablet, oral solution and intravenous injection that are approved for adjunctive treatment of partial onset seizure, myoclonic seizures, and primary generalized tonic clonic seizures in various pediatric age groups as well as in adults. The oral extended release tablet is specifically approved for adjunctive treatment of partial onset seizures, in adult and pediatric patients 12 years and older.

The Pediatric Safety Review for Keppra has come before this committee before. The basis for the current review is really the approval of levetiracetam injection as well as the extended release formulation.

The injection formulation or route of administration was approved in adults in 2006. The labeling was updated with pediatric data in 2014, so about eight years later. And the safety and effectiveness of this route of administration was supported by PK data in adults and children, and efficacy and safety data in controlled pediatric studies using oral levetiracetam. So, efficacy was extrapolated.

As I mentioned, the other basis for this safety review is the approval of the XR formulation in pediatrics. The adult approval was in 2008, and the labeling was updated with pediatric information in 2014. And similar to the injection formulation, safety and effectiveness in patients 12 years and older, was supported with PK data, with this formulation, in adults and adolescence, and efficacy and safety data in controlled pediatric studies using the immediate release levetiracetam.

This is just a list of the adverse events. These are known adverse events that appear under warning and precautions. And these include behavioral abnormalities and psychotic symptoms, suicidal behavior and ideation, somnolence, anaphylaxis; and specifically, in pediatric, patients less than four years of age, increased diastolic blood pressure. Other pediatric-specific adverse events, that are included in labeling, include fatigue, aggression, nasal congestion, decreased appetite and irritability.

And for the next couple of slides, I'll go over the utilization data to give some context to the adverse events that I'll be discussing later in the presentation. This first table provides the nationally-estimated number of patients who were dispensed a prescription for levetiracetam from outpatient retail pharmacies from August 2014, to December 2016. And during this time, as you can see, pediatric patients, less than 16 years of age, comprised approximately 16 percent of all patients who received extended release oral levetiracetam. So, it's the bottom part of the table here.

The second table is based on data that represents the nationally estimated number of patients, with a hospital discharge billing, for levetiracetam oral and injectable products, from August 2014, through December 2016. Pediatric patients, age 16 years or younger, comprised 6 percent of all patients with a discharged billing for oral levetiracetam, and 8 percent of all patients with a discharged billing for injectable levetiracetam. The patient population described in these two slides may overlap, given that one slide is for outpatient retail, and the other slide is for hospital, which accounts inpatient and outpatient hospitals. But I also want to remind the committed that the data does not include used data from stand-alone pediatric hospitals; and that may impact the numbers that you see specifically for the injectable levetiracetam.

So, moving on to the adverse event reports. There was a total of 470 serious pediatric adverse events that were reported during the period of May of 2013, through December 2016. Out of these, 28 resulted in fatalities. Out of the total pediatric reports with serious outcome, which were 470, 194 were excluded for the reasons that you see listed here. A good majority were duplicate reports, and there were about 19 cases of transplacental exposure, and two that were miscoded. For the remainder of the presentation, I'll focus on the 276 pediatric cases, which included 22 fatalities.

So, in general, the adverse events that were reported in cases, in greater than or equal to five cases, were known risks that are well described in labeling. And we have them

listed here. And these include behavioral abnormalities and psychotic symptoms, somnolence and fatigue, GI adverse events, dermatological and allergic reactions, movement disorders, sleep disorders, coordination difficulties or dizziness, hematologic abnormalities and suicidal behavior and ideation.

Going on to the fatal adverse events, as I mentioned, there were 22 fatalities. None of the cases provided evidence of a causal association with the product or levetiracetam, specifically. All cases reported alternative etiologies and did not provide adequate information for causality assessment. And in addition, 12 out of the 22 cases reported concomitant use of other antiepileptics. The 22 fatal adverse events included five cases of seizures, three cases of SUDEP, 10 cases of HIE, three cases of respiratory failure and one case of meningoencephalitis.

There were non-fatal serious adverse events that I mentioned. Some of the unlabeled adverse events were consistent either with the underlying disease or the indication of use. And events that were reported in greater than or equal to five cases included seizures, that the drug was ineffective or that the condition was further aggravated, problems related to product substitution and off-label drug use.

There were other serious unlabeled events that were further investigated. There were four cases of cardiovascular events, and these included two cases of cardiac arrest after an intentional overdose. And both patients were overdosed on multiple products. Hypotension; again, after an intentional overdose. There was a neonatal patient with pre-existing PVCs who had increased PVCs. There was one case of rhabdomyolysis, one case of encephalopathy and one case that was reported as neurophysiologic abnormalities.

This really concludes the safety review for levetiracetam. Most of the cases included non-adverse events in patients that had complicated or patients who had underlying medical conditions. All the safety events were known adverse events that are already labeled, so no new safety signal was identified. The agency plans to monitor for cardiovascular events,

rhabdomyolysis and encephalopathy in all populations, so pediatric and adults. Therefore, we recommend continuing ongoing surveillance. And the question back to you is, does the committee concur?

DR. WADE: We are open for comments or questions. Dr. Hoehn?

DR. HOEHN: I have a question about the 10 deaths related to hypoxic-ischemic encephalopathy (HIE), and I know you're limited by the data that you have. But I wondered if any of those were from refractory (inaudible), or if you knew any other information, since HIE is more of a descriptive term than causal term.

DR. MULUGETA: And I can defer to the safety reviewer, but eight out of the 10 cases were literature reports and there was very limited patient-specific detail that were provided. And maybe the safety reviewer can comment on the other two.

DR. HOEHN: While you're preparing for that comment, I'm just wondering how many of those were neonatal HIE. I don't know if you have that information.

DR. LONG: There was a literature report for, I believe, eight infants. And it was a study for levetiracetam for treatment of seizures and neonatal hypoxic ischemic encephalopathy. The study didn't really have much information besides the patient's head, HIE, and they didn't fair well.

There is no information about time to onset, causality association, so we really couldn't assess the association of levetiracetam with the disease. And the authors basically said that the cause of death was associated with the HIE and not with levetiracetam administration.

DR. MULUGETA: And then maybe to answer your question about how many were neonatal patients; the eight were reported as being neonatal patients. One was a nine-month-old and the last one was an eight-day-old. So, nine out of the 10 were neonates.

DR. WADE: And I would assume that the eight neonates had HIE prior to receiving levetiracetam. Was that clear in the report?

DR. MULUGETA: That's correct.

DR. CAMPBELL: So as a surgeon in the room, I'm curious about what the neurophysiologic abnormality during the craniotomy was -- what that means.

DR. LONG: In your packet, in the review -- page 20. So, on page 20, is a description of what happened in the case. It was a literature article that was published. Basically, the patient was having a craniotomy and tumor resection and they were monitoring the transcranial electrical motor-evoked potential signals. And when they received the levetiracetam, the first dose -- it looks like, 30 minutes during the dose, there is an abrupt global decrease in the transcranial electrical motor-evoked potential signals when they gave that. They stopped the infusion at that time, and the signal went, I guess, back to baseline. I'm not a neurologist. I don't understand what the signals actually mean. But it went back to baseline and it remained stable throughout the remainder of the surgery.

And then, at the end of the surgery, they completed the infusion that they started. And again, they saw another decrease in the amplitude. And when they stopped the infusion again, it went back to normal. And the patient didn't have any type of neurological deficits after they received the dose. But it was something that they saw during this tumor resection.

I did check the database for any other reports of this phenomenon in pediatrics and adults, and there were no other cases. So, this was a very isolated case of this, and it was very specialized. And it was during a craniotomy, during tumor surgery, where they gave this medication and were monitoring this specifically.

DR. TURER: That's the mechanism by which I believe the child with congenital heart disease got picked up as having coronary artery stenosis and ischemic cardiomyopathy, simply because they were being monitored. And I think, probably with a lot of these drugs, we don't monitor things. We don't cath children. We don't do cardiac echos on them. But if we did, we may find stuff like that.

DR. LONG: I can tell you that most of the reports that I see with levetiracetam, any type of neurological monitoring abnormality, I guess, is just EEG abnormalities. So, they'll see something with an EEG abnormally. And those are the majority of the cases in pediatrics and adults that we see. And again, I agree; if you don't monitor the patient, you don't know what's going on.

DR. WHITE: I would respectfully say that congenital coronary artery stenosis is not usual in children with congenital heart disease, depending upon their primary diagnosis. And in the absence of a report that this was atherosclerotic disease, I don't think we can blame this on metabiotic causes.

DR. WADE: Are there any other comments? Can we have the voting slide back up, please? In conclusion, then, of the Focus Safety Review, most cases included known adverse events in patients with underlying medical conditions, and no new safety signals were identified. The plan is to monitor for cardiovascular adverse events, rhabdomyolysis and encephalopathy in all patient populations, and the FDA recommends ongoing surveillance. The question to the PAC is, do you concur with this recommendation? Voting is open.

COMMITTEE VOTE - KEPPRA

DR. WADE: Okay. The vote is 14 yes, zero abstain, zero no. If we can go around the room from the left to ascertain your vote.

DR. CAMPBELL: This is Jeff Campbell, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy Turer, I concur.

DR. FISCHER: Gwen Fischer, I agree.

DR. HAVENS: Peter Havens, I concur.

DR. CUNNINGHAM: Melody Cunningham, I concur.

DR. CATALETTO: Mary Cataletto, I concur.

MS. CELENTO: Amy Celento, I concur.

DR. WHITE: Michael White, I agree.

DR. NEVILLE: Kathleen Neville, I concur.

DR. CALLAHAN: David Callahan, I agree.

DR. MCGOUGH: James McGough, I agree.

DR. DRACKER: Bob Dracker, I concur.

DR. HOEHN: Sarah Hoehn, I concur.

DR. WADE: Thank you very much, everyone. We will now move on to Contegra Pulmonary Valved Conduit with Dr. Vega.

CDER – STANDARD REVIEW OF ADVERSE EVENT - CONTEGRA

DR. NELSON: We just need a moment to rotate the team at the table.

DR. WADE: Yes. So, the shift here is getting the device representatives up.

DR. NELSON: And as they're settling in, perhaps you can ask the CDRH colleagues to introduce themselves.

DR. WADE: Can the new colleagues at the table, from the device area, introduce themselves?

DR. PEIRIS: Vasum Peiris. I'm the chief medical officer for pediatrics and special populations for the Center.

DR. LIU: This is Jenny Liu, CDRH Post-Market Surveillance.

DR. AGGREY: George Aggrey, epidemiologist, Office of Surveillance and Biometrics.

DR. WADE: Dr. Vega, thank you for providing these presentations.

DR. VEGA: Thanks to you. Good morning, everyone. My name is Dora Vega, Medical Officer in the Division of Epidemiology, Office of Surveillance and Biometrics, CDRH. And today I will present a summary of the Fourth Annual Post-Market Safety Report for the Contegra Pulmonary Valved implant or device, which comprises MDR data, and literature data, and was provided by the offices of the Center.

The Contegra Pulmonary Valved Conduit is a bovine implant, approved in November 2003, for the correction or reconstruction of the cardiac congenital malformations listed below, and for replacement of dysfunctional pulmonary homograft conduit.. The Annual Distribution Number for the Contegra device is 4000. Since the last year of PAC, a total of 372 units were sold, and 172 were implanted, of which at least 163 devices were used in pediatric population.

Next, I will present a summary of the medical device report received by FDA since the last PAC meeting. A total of 109 MDRs, associated with Contegra, has been received from June 1, 2016, to May 31, 2017. However, the number of unique reports is 84 after removing events presented in previous PAC meetings, and all published in the literature, which will be discussed later in this presentation. The 84 unique reports, included one pediatric death and 83 injuries. As a note, 83 of the 84 MDRs reported the patient eight, and included 81 pediatric subjects of mean age 9.8 years.

This slide, which also appear in your executive summary, reported 81 pediatric MDRs by primary event. Note: The time to event occurrence, or TTEO, was considered at the time between device implant and occurrence of the adverse event. The top event reported were stenosis and device replacement. Stenosis was the adverse event most frequently reported in pediatric patients, representing approximately 44 percent of the cases. All of them required device replacement or angioplasty. The 35 MDRs indicated in device replacement did not mention a stenosis nor the specific reasons.

This slide provides new information recently provided by the suspected tracheal compression case mentioned in the previous slide. The patient was a male neonate with a history of Truncus arteriosus type II, corrected with a 14-millimeter Contegra implant, using a Rastelli type procedure. The patient required a conduit replacement, two weeks post Contegra conduit implantation. Issues reported, prior to conduit replacement, include high mean airway pressure, MEAP, and suspected tracheal compression. Patient expired six days after Contegra replacement. Cause of death of the patient was pneumonia and sepsis. The physician's report states the patient's death was not related to the Contegra device.

When compared with this year MDRs, those reported to the 2016 PAC, most of the events were similar, even though patient's age variation and the number and percentages may differ, are suspected with a passive reporting system. The only new event identified in the current review is the discussed case of potential tracheal compression.

Now, I will present a summary of the literature review. This slide summarizes the literature review process, including the retrieval and selection of articles that resulted in one case report for final review. The search was conducted in the PubMed and Embase databases, by using the same key word as last year.

The case report article was discussed in detail in executive summary. Therefore, I will only highlight some of the most important points in the next few slides. The case report was by Falchetti et al., and described patients treated in Belgium. The authors reported that a 12-milimeter Contegra conduit was free from failure for 16 years after implantation. The case consists in a four-month-old patient, referred from another country with diagnosis of type 1 truncus arteriosus, or TA, large Ventricular Septal Defect, VSD, Right Ventricular Hypertrophy, RVH, right-side aortic arch, grade 2/4 truncal valve regurgitation, and a 9 mm diameter pulmonary artery, or PA.

The RVOT, or right ventricular outflow tract, was reconstructed with a 12 mm Contegra conduit implant. The ratio between the conduit and the 9 mm diameter pulmonary artery resulted in a mismatched Z-score of positive 2.5. The patient was discharged at 16 post implant.

Before that, I would like to go back if we can to the prior slide, please. I would like to note a couple of issues. The author noted that factors that may have played a role in the unusual longevity of the Contegra 12 mm -- and this is part of the discussion in the paper -- included moderated positive 2.5 Z-score of the device oversizing and the distal everting suture technique used, potentially contributed to avoidance of distal stenosis.

Sixteen years after implantation, the patient was referred back to the original surgical team for reoperation due to conduit failure. The examination shows a 16-year-old female, weighing 73 pounds, and 5' 2" high, with no signs of right ventricular compensation. Transthoracic echocardiography shows competent pulmonary valve. Conduit stenosis with pressure gradient of 110 mmHg across the right ventricular outflow track, with no evidence of regurgitation and normal right and left ventricular function.

CT scan show conduit diameter shrinkage of 9 mm. Pulmonary artery resulted in a mismatch of Z-score of positive 2.5, and the patient was discharged on postoperative day 16 for follow-up of the referring country.

FDA conclusions at this time -- and I apologize for the overlapping on some data due to the slide. Therefore, the conclusion of FDA for the current review period are, MDR data review identified a case of conduit replacement for unclear reasons. The FDA believe that, currently, there is insufficient information to determine if this was a case of tracheal compression due to the device. Other adverse events identified in MDRs are known events, addressing the device labeling, and no new safety concerns were reported in the literature.

In summary, the Food and Drug Administration proposes to continue the conversation with the manufacturer for additional information regarding the suspected case of tracheal compression, and to continue device surveillance of the annual distribution numbers, MDR data, literature review to report to the PAC in 2018.

Now, the questions to the PAC are; first, does the committee agree with FDA conclusions and recommendations to continue device surveillance and report the annual distribution number, MDR data, and literature review to the PAC in 2018? And second, does the Committee have any additional comments? Thank you.

DR. WADE: Are there questions or comments from the Committee? Dr. White?

DR. WHITE: The case of the tracheal compression, I'm not sure is all that outstanding. It's mostly a mechanical problem and it's probably due to the placement of the conduit in the first place. If there was an aneurysmal dilation, that's of concern but that's a known complication. So, I think it's just a mechanical problem of where they put the conduit.

As to the 16-year-old with the particularly longevity, echo frequently under or over estimates the gradient across the valve. And we know that pulmonary stenosis is well tolerated by the right ventricle over a longer period of time. That conduit probably should've been replaced sooner. But again, I don't think that's a particularly outstanding observation.

DR. VEGA: Yes. I agree with you. Personally, we conclude the same. Certainly, we cannot think about the possibility of dilatation, which is the term or the terminology used in the labeling of the device. Certainly, example (inaudible), right? It could have happened. However, there are other reasons, a lot of reasons for us to believe that not necessarily was a mechanical cause.

Another reason could be that the patient was -- definitely being in the hospital under surgical procedures -- was under respiratory assistance. It could have had just -- I don't know, in my mind -- a trauma of the pulmonary parenchyma, right? At the end, has a sepsis or

pass, of sepsis, which may represent or tell us that there was an involvement of the aveolar ventilation, which could be open to this anyway.

We have different possibilities at this time. We need more information. It's one single case, the one that came to us, the one that was reported in the surveillance. And therefore, we conclude that it needs additional conversation with the manufacturer to find the reason of this. In addition, the case was a Vietnam case. The information was very limited since the beginning, although the team participate in a number of interactions with the company. Probably, we received three or more letters. Jenny, if you can assist with this, I will really appreciate it. If you would like to add something on this. But we did not get more information.

DR. WHITE: No. I don't think additional discussion as necessary at this time.

DR. VEGA: Okay. Thank you very much.

DR. WHITE: Thank you.

DR. WADE: Dr. Sayej?

DR. SAYEJ: I just have a question and a comment. I'm looking at the data of the primary reported events by patient, and there were 35 reports of devices replaced without any reasons provided. Is this because the expectations of the life expectancy of these devices is short, and therefore, they need to be replaced on regular basis, or is this because there were actually some events that happened that required the replacement?

DR. VEGA: I would like just to refer this just to the premarket to make sure.

DR. PEIRIS: Let me try to help to facilitate the conversation here. The simple answer to your question is yes. We expect that, with many devices, when they're put into smaller patients, as the blood volume grows, heart grows, everything grows, there is going to be stenosis.

We expect replacement as a field in congenital heart disease. We are trying to develop techniques and methods by which to reduce the amount of times we intervene. But

aside from these global changes, a simple answer to your question is yes. Even if there is no device-specific failure, in terms of the conduit working as it's supposed to, there will likely have to be upsizing.

DR. NELSON: And just for the record, that was Vasum Peiris, who happen to also be a pediatric cardiologist.

DR. WADE: Last question, Dr. Havens.

DR. HAVENS: But the case report that was noted in the Hickey (phonetic) article that was referenced specifically point out using a Z-score plus one to two when choosing the conduit. Does FDA weigh into those kinds of details when they evaluate or make recommendations on the use of these devices, since that would be a very specific kind of issue?

DR. PEIRIS: Yes. So, let me just back up a little bit as well. The intent of that presentation about the 16 years freedom, from conduit failure, or "failure" was just intended to be a presentation of a very unique event since one of the concerns is always that these devices are replaced earlier and earlier. To answer your question, specifically, about Z-score valuations, the FDA is not weighing into what type of sizing a physician should use to place a conduit.

The point about the Z score was merely to imply that the authors of that paper suggested that an upsizing of 2.5, based off of body surface area for that patient, perhaps had an association with longevity of that conduit. As was already alluded to, that conduit likely needed to be replaced earlier, and the RV did have some signs of potential dysfunction.

DR. HAVENS: No. This was related to the Hickey article that was in the background information that was supplied, where they make a recommendation of upsizing as well.

DR. PEIRIS: The FDA is not making a recommendation in terms of sizing for the conduits.

DR. WADE: Dr. White, and then we'll vote.

DR. WHITE: Just a very quick comment. This is a practice decision made at the time of surgery. You put in a conduit as big as you possibly can in the patient, depending upon the anatomy that's available for working with. And, I think that's all.

COMMITTEE VOTE - CONTEGRA

DR. WADE: Can we have the question slide up. Does the committee agree with the recommendation about continued surveillance and reporting in regards to the Contegra conduit? Voting is now open. Vote is 14 yes, zero no. If we can start on the left.

DR. CAMPBELL: Jeff Campbell, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy Turer, I concur.

DR. FISCHER: Gwen Fischer, I concur.

DR. HAVENS: Peter Havens, I concur.

DR. CUNNINGHAM: Melody Cunningham, I agree.

DR. CATALETTO: Mary Cataletto, I concur.

MS. CELENTO: Amy Celento, I concur.

DR. WHITE: Michael White, agree.

DR. NEVILLE: Kathleen Neville, I concur.

DR. CALLAHAN: David Callahan, I agree.

DR. MCGOUGH: James McGough, I concur.

DR. DRACKER: Bob Dracker, I concur.

DR. HOEHN: Sarah Hoehn, I concur.

DR. WADE: Thank you everyone. We will now move on to the Enterra Therapy Systems and continue with Dr. Vega.

CDER – STANDARD REVIEW OF ADVERSE EVENT - ENTERRA

DR. VEGA: Hello everyone, again. I'm Dora Vega from the Division of Epidemiology, Office of Surveillance and Biometrics. And I will present a summary of the Fourth Annual Post market Review Data, this time for the Enterra System.

Okay. Enterra is indicated for chronic, intractable nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology in patients 18 to 70 years old.

The Enterra Annual Distribution Number for this reporting period has not exceed the 4000 approved units. The number of units sold were 1,865 neuro-stimulators and 2,462 leads. And the number of devices implanted in pediatric patients reached a total of 93 units, 56 first device implants and 37 as device replacements.

Following a standard procedure for analysis, an MDR data search was conducted for the Enterra system, product code LNQ for the period from May 1, 2016 to April 30, 2017. The search resulted in 404 total MDRs, comprising 15 pediatric patients, 271 adults, and 118 cases of not-reported age.

This table shows the number of MDRs by event type and age group. The MDRs were excluded from the total 404 numbers, since the events were previously reported in articles outside of the time window for this analysis. Therefore, there were 401 unique reports in the current period, including two deaths, 255 injuries and 144 malfunctions.

In the next slide, I will provide additional information regarding the 15 total pediatric patients. This table shows the time to event occurrence in 294 MDRs, including all 15 pediatric patients. The event in adults in indeterminate age more frequently occurred within one to five years of implants, while all pediatric TTEO fell within the first 21st month of implants, suggesting early onset of adverse events such as postoperative infections, return to symptoms, and abnormal abdominal contractions.

DR. WADE: Can you pause for a moment? We lost the microphone.

DR. VEGA: If you can go back to the prior slide. This table identify the most commonly reported problems, both, patient and device combined in pediatric MDRs compared to last year's finding. Last year, the complaints most often reported were electrical shock, inappropriate, due to high impedance level.

This year's new finding centered on therapeutic response decreased/paresis, in red characters, that can relate with occurrences of nausea, vomiting and abdominal pain, discomfort in MDRs. These findings may be related to an increased number of MDRs of lead malfunctions such as device impedance, lead connection and/or battery, testing adjustment, device settings and repositioning of the device and lead revisions that require intervention and hospitalization.

Manufacturer evaluation of these devices was limited due to that the devices were not returning in 352 of the 401 MDRs. Infection and erosion show similar complaint incidents to last year. The root cause of these events was not reported and they were concluded by the manufacturer as known inherent risk of procedure.

In conclusion, both patient and device problems in pediatric patients were similar to those observed in adults and indeterminate aged patients. While the reported problems are known as inherent risks for the device, and do not represent any new concerns for patient safety, it was noted an increasing trend of device malfunctions related with leads, connection and battery issues. In most cases, 352 of the 401 MDRs received, these devices were not returned to the manufacturer for evaluation.

A literature search review for Enterra was also conducted to address the probable benefit for the improvement in upper GI symptoms, with action in need for (inaudible) support, and the improvement in gastric emptying time, and the adverse event for safety.

As seen in the slide, the literature search for Enterra was conducted in PubMed and Embase databases using the terms listed here. The data search was limited to human

clinical studies in pediatric populations, and also published between May 1, 2016 and April 30, 2017.

The results show 124 citations that were further evaluated for eligibility resulting in 123 articles, included for the reasons provided in the executive summary. And these conclusions, at the end, resulted in one article published by Lee et al. for field review and assessment.

The paper by Lee et al. consist in a systematic literature review on neuromodulation treatment and modalities. For autonomic disorders such as gastric electrical stimulation, or GES, and gastroparesis, GP, among others. The authors identified four papers that report gastric electrical stimulation for the treatment of gastroparesis. However, only two papers, Abell et al. and McCallum et al., include pediatric patients.

Of note, both papers are beyond the time scope for the current review periods as they were published in 2003 and 2010, respectively, and reported in the 2014 PAC meetings. However, we decided to provide a brief summary of them as follows.

This slide summarizes the study design of Abell et al. and McCallum et al. clinical trials. Both studies have similar crossover designs, with a slight difference, such as patient sample size, 35 and 55 subjects. Patient sub-cohort by medical conditions, such as diabetic, idiopathic and refractory diabetic patients. (Inaudible) crossover are not on treatment period, only McCallum study has this on face. And the length of the study faces, one or two months, crossover period, and 10 or 4.5 months follow-up period.

This slide shows a summary of the results of both studies reporting as probable benefit, that patients in on-therapy mode have an increased reduction in median vomiting frequency; along with an improvement in the severity score, and overall symptoms, compared with patients in off-treatment mode, with the greatest benefits observed in the diabetic cohort. And gastric emptying was reported to be modestly accelerated or unchanged. From a safety

perspective, these studies report that the most common patient-related adverse event were hospitalizations associated with gastroparesis symptoms, which accounted for approximately 33 percent of the adverse event; and ketoacidosis, vomiting, hematemesis and hypoglycemia, among others.

The most common device therapy-related serious adverse events comprised device explant due to infection, stomach performation-1 and a skin erosion-1, and lead migration, dislodgement, leading to surgical intervention. And a total of seven deaths, five cardiovascular, cerebral (inaudible) and one (inaudible) infection sepsis. None of them charged to be device or therapy related.

Overall, the literature review suggests as probable device benefit, an improvement reduction of upper gastrointestinal symptoms, such as vomiting. The effects of the need for nutritional support was not evaluated, and additional surgery may be required due to lead connection battery issues. From the safety perspective, device-related adverse events were similar to those identified in previous literature reviews, as well as in the product labeling, except hematoma, one case, and do not raise new safety concerns. Also, the current literature review has several limitations that we need to note.

Only one paper met search criteria. There were study design factors and questionable level of scientific evidence, which may affect the study's results and conclusions. And it is unclear if the device benefits reported in the overall patient population reflected the pediatric cohort in the study. Overall, there is limited ability to draw concludes about the probable benefit and safety of Enterra for pediatric population.

Based on the reported data, we recommend continued surveillance and report the finding of annual device numbers, MDR data and literature review, to the Pediatric Advisory Committee in 2018. Therefore, the question to the PAC is, does the Pediatric Advisory Committee agree with our conclusions and recommendations? Thank you.

DR. WADE: Dr. Hoehn?

DR. HOEHN: Yes. I have a question about slide number 4.

DR. VEGA: What slide?

DR. HOEHN: Four.

DR. VEGA: Number four. Yes.

DR. HOEHN: Slide Number 4. On that slide, you said there were 19 new devices in people under 18 years of age, and 37 were placement devices in pediatric patients. And what I wanted to know is, do we know what the age breakdown was. Are they mainly adolescence, 12 to 14-year-olds, or what is the age of the children who got these devices in 2016?

DR. VEGA: Sure. OSV, DPS could assist with this, the numbers, if there is any data?

DR. WADE: Yes. Let's have another question while we try to get that data point. Actually, Gwen was first. And then we'll go with you, Dr. Havens.

DR. FISCHER: Just a question about Slide 8, US therapeutic response decrease, and also some symptoms that may suggest that there is a therapeutic response decrease. Were those MDRs in conjunction with lead malfunction or connection malfunctions?

DR. VEGA: DPS, again, can assist with this.

DR. RICKETTS: A good number of them this year were because of that, yes.

DR. FISCHER: Thank you.

DR. HAVENS: The background information suggests that the company changed the wrench to make it torque sensitive. And that this may have led to the increase in problems with malfunction. Did they change back to a normal wrench?

DR. RICKETTS: I posed that question to Medtronic and they are supposedly looking into it. And I should get an answer by the end of the week on that. Basically, they just said, yeah, we're aware of that, we're looking into it.

DR. WADE: Do people feel like they can vote before we have the data to answer Dr. Hoehn's question? Can I ask a follow-up question, because maybe somebody on the committee knows the answer? Is there a minimum age or a minimum weight that they could do this device in?

DR. WHITE: I don't have an accurate answer but, in-general, devices like this for pacemakers are limited by the subcutaneous tissue and the ability not to have dehiscence of the wound. So, it's sort of a decision made by the surgeon who's implanting the device, if there's enough tissue or not in order for the device to sit there safely.

DR. VENKATARAMAN-RAO: In the literature that we have reviewed, in prior PAC meetings, some of the articles have gone down to an age of three or four years of the youngest that the device has ever been used in.

UNIDENTIFIED MALE: So, regarding the question about the 37 pediatric patients; unfortunately, that was the only information we were given by Medtronic. They didn't give us a breakdown.

DR. VEGA: Thank you very much.

COMMITTEE VOTE - ENTERRA

DR. WADE: Let's go ahead and move forward with the vote. If we can have the prior slide, please. The conclusion of the device presentation was that they would continue ongoing surveillance. And, does the Committee agree with the CDRH conclusion and

recommendation? The voting is open. 14 favorable, zero abstain, zero negative. If we can start on the left.

DR. CAMPBELL: Jeff Campbell, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy Turer, I concur.

DR. FISCHER: Gwen Fischer, I concur, but would also add that if the FDA could maintain communication with the company regarding the manufacturing evaluation as you've stated in Slide 9 that, that would be good to follow-up on. Thanks.

DR. HAVENS: Peter Havens, I concur. And I'll be interested to hear what the wrench shows.

DR. CUNNINGHAM: Melody Cunningham, I agree.

DR. CATALETTO: Mary Cataletto, I concur.

MS. CELENTO: Amy Celento, I concur.

DR. WHITE: Michael White, agree.

DR. NEVILLE: Kathleen Neville, I concur.

DR. CALLAHAN: David Callahan, I agree.

DR. MCGOUGH: James McGough, I agree.

DR. DRACKER: Bob Dracker, I concur.

DR. HOEHN: Sarah Hoehn, I concur. Since this information is from the manufacturer, it should be very obtainable; so, I would like to request that the next time we look at it, they do include age and weight, just so we can track if they started expanding into younger kids or under 10 kilos or things like that. And we should be able to get it since it's submitted from the manufacturer. That's my only request, is that next time, they include that data for us.

DR. WADE: Thank you everyone. While Dr. Vega has the podium, we're going to switch around the order, just trying to make up some time and have Dr. Vega present an expedited review focused on the Elana Surgical Kit.

CDER – STANDARD REVIEW OF ADVERSE EVENT - ELANA

DR. VEGA: Once again, thank you very much. I don't know if it's good morning or afternoon at this time. But, again and again, I'm Dora Vega from the Division of Epidemiology, Office of Surveillance, CDRH. And I will present summary of the Fifth Annual Post market Review Data, in this case, for the Elana Surgical Kit.

Here, an update of the device Post market data since the previous 2016 PAC meeting. We are unaware of sales or use of the device. There have been no medical device reports, MDR, associated with the device. And there have been no new peer-review publications related to Elana during the current reporting period.

Therefore, the review conclusions for the current year are, no new safety concerns have been identified, by FDA, since the September 2016 PAC meeting. The probable device benefit and risk profile for the pediatric population continues to support the HDE. And, the Mandated Post-Approval Study has been put on hold due to non-use of the device in the United States. Should device use resume, the study will be reinstated.

Based on the current status of the Post market data for the Elana Surgical Kit, we recommend continued surveillance of the annual device numbers, MDR data, literature review. And as mentioned before, should device use resume, the post-approval study will be reinstated.

Consistent with this, the questions to the PAC is, does the Committee agree with FDA conclusions and proposed approach? Thank you.

COMMITTEE VOTE - ELANA

DR. WADE: Since there were no devices distributed, are there any questions or comments? Otherwise, we'll move forward with the vote. Voting is open. Again, we have 14 favorable, zero contrary. We'll start on the left.

DR. CAMPBELL: Jeff Campbell, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy, I concur.

DR. FISCHER: Gwen Fischer, I concur.

DR. HAVENS: Peter Havens, I concur.

DR. CUNNINGHAM: Melody Cunningham, I agree.

DR. CATALETTO: Mary Cataletto, I concur.

MS. CELENTO: Amy Celento, I concur.

DR. WHITE: Michael White, agree.

DR. NEVILLE: Kathleen Neville, I concur.

DR. CALLAHAN: David Callahan, agree.

DR. MCGOUGH: James McGough, agree.

DR. DRACKER: Bob Dracker, I concur.

DR. HOEHN: Sarah Hoehn, I concur.

DR. WADE: Great. We will now move on for a discussion of Pleximmune with Dr. Courtney Lias.

CDER – STANDARD REVIEW OF ADVERSE EVENT - PLEXIMMUNE

DR. NELSON: Kelly, while Courtney is getting settled, let me just say that was a poster child in my mind for web posting. No data.

DR. WADE: I agree.

DR. NELSON: Somewhere in between, we'll figure out the other criteria, but that one's pretty straight-forward.

DR. LIAS: My name is Courtney Lias. I'm with the Division of Chemistry and Toxicology Devices and CDRH's Office of In Vitro Diagnostics. This is an update on the Pleximmune system. The Pleximmune test is an in vitro diagnostic test. That is a laboratory test done to assess the risk of acute cellular rejection in children with liver and small bowl transplants.

Pleximmune was assessed as having the ability for running less than 4000 tests per year, and many more less than that per year typically run. During the reporting period that we are talking about today, which is June 1st of 2016 through May 31st of 2017, there were 315 Pleximmune tests run and that was on a total of 231 patients. There were no adverse events during this time period. And our review team also assessed information from outside sources, such as literature and other potential databases, and we found no signals reporting any potential adverse events since the last PAC meeting.

We conclude that the probable benefit risk profile of the device, for this population, continues to support the HDE for which the exemption was granted. And we recommend continued surveillance, and we'll report to the PAC in 2018, the annual distribution number, MDR review and the results of our literature review. So, our question for the PAC today is, does the Committee agree with our conclusions and recommendations for the Pleximmune test. Yes?

DR. HAVENS: Out of the 231, what total number of transplants does that represent in the country? Is this a commonly used test?

DR. LIAS: I don't believe it's a commonly used test. It's obviously less than the full number, but this is a local test also, it's run out of Pittsburgh. And so it would be the sample sent, probably, from people within contact of that laboratory.

DR. HAVENS: Thank you.

DR. NELSON: Just a comment. One of the things that we talked about -- I don't know if it was two years ago or whenever it was -- was, how one evaluates the safety of an in vitro diagnostic device. And it's probably not through MDRs. So, we're sort of discussing that as a topic. And whether we'll ever mature that into a discussion or not, I don't know. But this is a test that's just used in mainly one location.

DR. LIAS: I would add that it's a highly adjunctive test, used along with a lot of other clinical signs and symptoms, and wouldn't typically be used alone to make any decisions.

DR. NELSON: And, when it was first presented, it was unclear the impact it had actually on the clinical decision-making. As I said, it was adjunctive. The clinical decision-making was being made on other reasons, as well. So, it's an open question as to how one would evaluate the safety of this device, compared to how one would evaluate the safety of the other devices.

DR. SAYEJ: Is this device approved for adults too, or no?

DR. LIAS: No; only children.

DR. SAYEJ: Is there a reason for that? Just curious.

DR. LIAS: They only sought approval for children.

DR. JONES: I think, also in the line of how do you evaluate safety, but what would even prompt providers to report an issue? I mean, if they felt maybe the results didn't improve their diagnostic abilities? I don't think most people would be prompted to even report that.

DR. LIAS: I mean, we did have a little bit of this discussion a couple of years ago. For all in vitro diagnostics, we do MDR analysis. And it varies across test how much the MDR is informed; the ability for surveillance for many in vitro diagnostic test that is useful. The more adjunctive the test is, the harder it is to assign a test error to an adverse event. So, the more adjunctive, the less likely you are to actually attribute an adverse event to the test result.

COMMITTEE VOTE – PLEXIMMUNE

DR. WADE: Is there a voting slide? Does the Committee agree with the FDA's conclusion and recommendation to continue their ongoing surveillance? The vote is 14 favorable, zero contrary. We'll start on the left.

DR. CAMPBELL: Jeff Campbell, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy Turer, I concur.

DR. FISCHER: Gwen Fischer, I concur.

DR. HAVENS: Peter Havens, I concur.

DR. CUNNINGHAM: Melody Cunningham, I concur.

DR. CATALETTO: Mary Cataletto, I concur.

MS. CELENTO: Amy Celento, I concur.

DR. WHITE: Michael, white, yes.

DR. NEVILLE: Kathleen Neville, I concur.

DR. CALLAHAN: David Callahan, I agree.

DR. MCGOUGH: James McGough, I agree.

DR. DRACKER: Bob Draker, I concur.

DR. HOEHN: Sarah Hoehn, I concur.

DR. WADE: Thank you very much. So, we'll move on now to our last device discussion. I would recommend that everyone, though, stay alert and engaged. We will end today with the Kidnet Trajectory Update, which I think will be exciting. And we'll move on now to our Berlin Heart EXCOR device with a presentation by Dr. Peiris.

BERLIN HEART® EXCOR® PEDIATRIC VENTRICULAR ASSIST DEVICE (VAD)

DR. PEIRIS: Hi, everybody. Everybody's still awake, excited about the last presentation here? Oh, second to last. The last device presentation, because that's what we're really interested in here. This will take approximately 25 minutes. I'm joking. The Berlin Heart EXCOR device has moved from HDE to a PMA, and will no longer come to the PAC for review, as part of guidelines.

DR. WADE: And That's because of the number of devices being used in clinical practice.

DR. PEIRIS: Happy to clarify this, so if people have questions. It's not specifically because of the number of devices being used in practice. The sponsors have submitted applications and data for movement from HDE to a PMA. The distinctions are safety and probable benefit versus safety and effectiveness. They have achieved the PMA approval, and for PMAs, there is no need to come for PAC review. Happy to go through more details if there are any questions.

DR. NELSON: As Ann begins to get herself situated, it's really that move from probable benefit to efficacy that takes you from the HDE and the PMA to where they have disseminate data to that extent. And so, they can now make a profit on every -- they don't need the exemption for the profit. At this point, they can go ahead and make the profits, so it's no longer fitting into the PAC remit, per se. This is not the first device that that's happened to.

DR. PEIRIS: There's four devices, in all of our history, of the HDE program that have gone from an HDE to a PMA. There are some differences, as Skip mentioned, in terms of profits and costs. But basic point for this group is that the Berlin Heart will no longer be coming to the PAC for annual review.

KIDNET TRAJECTORY: WHERE HAVE WE BEEN? WHERE SHOULD WE GO?

DR. WADE: So we are back on track timewise. I'd like to thank everyone for that getting us back on track. Our final presentation today is Dr. Ann McMahon on the Kidnet Trajectory, Where Have We Been? Where Should We Go?

DR. MCMAHON: So, I am Ann McMahon and I'm the Deputy Director of Science in the Office of Pediatric Therapeutics, and the director of Kidnet. I am a pediatrician with training in infectious disease, virology and epidemiology. And I've been the director of Kidnet since 2011, when Kidnet started.

I talked to the PAC, in 2012, about Kidnet; and at that time Kidnet was in its infancy. I now want to talk about the history of Kidnet, what it is, what we've done with it, and get your thoughts about where to go from here.

Kidnet evolved out of conversations among the PAC in 2008. As you know, data from the FDA Adverse Event Reporting System often lack consistent clinical detail and patient information. And FAERS does not provide a denominator. To supplement FAERS, the PAC recommended providing chart review data from pediatric hospitals. Kidnet started in 2011 to fulfill this role.

I'll give you a brief background on what we've done with Kidnet, both from the prospective of the tools for data collection and from the prospective of the subject matter that we've studied. In Kidnet Number 1, we've studied the use and adverse events associated with

octreotide and proton pump inhibitors in patients in the pediatric intensive care unit and the neonatal intensive care unit. The tool we were using at the time was a paper-based case report form, extracting data from paper charts or PDFs. And secondarily, these data were manually entered into an Access database, exported and analyzed.

And what did we find with Kidnet Number 1? The data were descriptive. We obtained information on PPIs and octreotide use in adverse events, in general. We then looked more specifically at mortality and causes of death, that were available in the charts, in patients that received octreotide.

There were 222 children administered octreotide in this study and 53 of them died. The slide shows the mortality rate by indication for individuals using octreotide. Notice that the mortality in post-surgical chylothorax patients in this sample was near 90 percent. Whereas, that, in hyperinsulinism patients was two percent. The cause of death was also assessed by chart review.

Kidnet Number 2 is on the topic of whether off-label use is associated with an increased number of adverse events, compared with on-label use. Here, we studied fentanyl and azithromycin. Two drugs among 135 most commonly used drugs, in the PICUs of one collaborating hospital, were fentanyl and azithromycin. Since antibiotics and analgesics are the most widely used off-label in pediatrics, these drug classes made sense to use in the study. In addition, fentanyl and azithromycin both have on- and off-label use in the pediatric population.

In Kidnet Number 2, we used electronic medical records, and this was the only methodological difference from Kidnet Number 1, but still used case report forms. We still manually entered data into an Access database, then exported it for analysis. This slide shows the preliminary results for Kidnet Number 2. We performed descriptive analyses and showed enhanced detailed data compared to Kidnet Number 1. We performed regression analysis. We

used a binary model with the outcome of serious adverse event, "yes or no" as the dependent variable and off-label use as the independent variable of interest.

Covariates that have been included in at least some of the regression models constructed are listed on the slide. In the case of fentanyl, off-label use was consistently associated with serious adverse events, whereas in the case of azithromycin, off-label use was not associated with serious adverse events.

So, the strengths of Kidnet Number 2, are the use of electronic medical records with resulting increase in sample size for at least some of the drugs studies, and more clinical detail. We also asked a more targeted question than we did in Kidnet Number 1. And so, that we were able to get closer to an answer in Kidnet Number 2. Also, fentanyl has a narrow therapeutic index; and this fact may have contributed to the observation that there was a greater likelihood of serious adverse events in the group with off-label use. Limitations of Kidnet Number 2 included the study design, which was a convenient sample and retrospective chart review.

Kidnet Number 3 focuses on quantifying renal adverse effects of intravenous acyclovir in neonates. The technology has moved forward. We are using centralized Research Electronic Data Capture, the automated system known as Redcap, for data entry at all sites. Sites either manually enter data into Redcap, and some variables are extracted from outlying hospital medical records and streamed into Redcap. Data is de-identified, centrally, and sent to the FDA.

Kidnet has evolved technologically. We are headed towards larger sample sizes in electronic data transfer, and we may lose some details in the database, for example, loosing text fields only in the medical records. We think supplementing with some chart review might make for a more well-rounded project outcome.

We are hosting a workshop soon on Big Data in Pediatrics on September 18th and 19th, in Silver Spring, to explore strengths and challenges of using big data in healthcare and pediatrics in particular. The title is, Advancing the Development of Pediatric Therapeutics Application of Big Data to Pediatric Safety Studies. We hope you all can attend either by WebEx or in person.

I'll now go over the strengths and weaknesses of Kidnet in general. Overall, Kidnet is used for providing detailed pediatric information. More recently, the sample sizes for some research studies have been sufficient to come closer to answering directed questions. And limitations of Kidnet are, the sample sizes are too small, as of yet, to answer many questions. And also, to date, Kidnet does not provide choices as to study design. It's simply cross-sectional.

Today we would like to ask you to discuss two questions. First, how should we refine Kidnet going forward? And second, what types of pediatric safety studies should we focus on using Kidnet? And I think I'm going to leave this slide up so people can be reminded of the questions. I'll sit down but I'll be at the table.

DR. WADE: Wonderful. Thank you for that excellent presentation. Would you like to start us off, Dr. Turer?

DR. TURER: Two things. It says that the data would be de-identified centrally and sent to FDA. I wonder if there's discussion about retaining an identifier so that you can link back to the charts. And the importance of this is the ability to probe potential biases, but also get more granular detail from cases. We know when we extract these data, a lot of times they'll be missing data fields or you extract the wrong field that's not a utilized one. Because, I do large secondary analysis extracting electronic health record data.

The second thing is, occasionally, verification bias. So sometimes labs are ordered on children that are undergoing a specific procedure, whereas those who are not

receiving that therapy or that device, do not. And so that can bias your data and want to make sure that you can address verification bias.

And then the reliance on billing codes, it is also another challenge. And so that ability to reconnect the dots to retain some central identifier, even if it means obtaining IRB approval from FDA and the involved sites, I think would be of great, great benefit. So, point number one.

And then, two, look at how to set things up in such a fashion that you can connect with adult electronic medical records and understand long-term outcomes. More challenges there, particularly with identifying things in the same patients over time; but that would be a pie-in-the-sky goal, I would think.

DR. MCMAHON: Thank you for those thoughtful comments. We do have identifiers that we retain. So, that in the case of the site that's primary for the Redcap, they are able to go back to the hospitals and the hospitals retain their own identifiers. So, it's done that way.

As far as long-term observational studies, I don't think anyone has yet really figured out the best identifier to use for pediatrics than adults. And it's further complicated by the fact that the identifiers that you would use would be personal information. I don't know if you have an idea about how to have an identifier that you could use long-term.

DR. TURER: There are some mathematical models where you can model the likelihood that you have the same patient based on a number of different identifiers, but they have to be validated. I'm working in my own health system right now so that I can connect the dots across the different health systems, and connect pediatric drug use conditions over time. And so, I've been working with people on some of these statistical models. But on a national level, the challenges are going to be far greater.

DR. SAYEJ: Just a couple questions regarding the first point, how should we define Kidnet going forward. Just looking at the Kidnet 1, 2 and 3, chart records, versus electronic medical records, verse Redcap. Redcap is phenomenal when you're inputting data going in a prospective manner. But it's probably not the most cost-effective way since every center will require to have some people inputting that data into Redcap. And to me, it sounds like electronic medical records would be the most ideal way, if we can make sure that all the different centers have the same variables that you're looking at inputted on every single patient. I'm not sure how you can do that.

But the second question I have is, is this something that's limited to those six or seven hospitals; or is this something that's potentially going to be expanded to include more hospitals so they have more data and more patients being included in these studies?

And lastly, regarding the identifier. I definitely agree with you that if there is an identifier that you can follow over time, that would be great. And again, I'm just being speculative here. I'm not sure where the Social Security number comes in, because that's a defined identifier on every patient. And I'm not sure if FDA wants to take responsibilities for these numbers getting out in the wrong hands. But I'm not sure if there's something similar that can be applied.

DR. TURER: One last point would be that wherever the central database is stored, it should not be on a computer that has access to the internet. So, it has to be offline.

DR. HOEHN: I just had a comment about the first one in terms of how you refine it, and it's similar to what other people said. But I didn't know if there were other efforts to involve other Children's Hospitals, or to connect it to a Children's Hospital database. Or, in the idea world, if you could connect it to every hospital that receives NIH funding, we would like you to participate in this.

And if there are ways that you could tie it to other things, that you could mandate it, then it would be a lot more useful. Otherwise, I'm afraid you can say, well in these six hospitals, this is what you observe, but I worry about the generalize-ability of it, given the current number of contributing hospitals.

DR. MCMAHON: We are interested in expanding, but are going very cautiously because of things like PPI. And also because I think it's very important to have some uniformity in the way the data is collected; and including, if we were going to use electronic medical records for most of what we collected. One of the issues is that some of the hospitals have informatics people that help, and others don't. And it depends on whether it's a research focus in that particular hospital, so it's gingerly. Yes?

DR. JONES: Along the lines of the electronic health medical records, I was just wondering has FDA engaged with any of the companies that design these health records, like Epic or Cerner. Because one of the things you mentioned was the difficulty with text fields. And so, a lot of times when trying to get data out of these health records, there are some fields that you can extract easily, but there's others where if it's text, it really hard to use that data.

I think, trying to engage them in the conversations of how they're building these systems, that could help facilitate research, would be important. Because I think, most times when they're built, they're built with clinical practice in mind. But I think there are some companies that are interested also in the research side of it. In your conference, later this month, I'm wondering are there any of these electronic health record companies that have been invited or are they participating at all?

DR. MCMAHON: Yes. We do have some representation of health record companies.

DR. JONES: Yes. I think that'd be great to try to talk to them more about how to build this software so we can use it both for clinical and for research.

DR. NELSON: Having been at the octreotide meeting, which, if I recall, was that 19-product meeting a number of years ago, part of the challenge here is Kidnet was designed to provide the sort of clinical detail that often the FAERs adverse events are lacking. And so, to the extent that one begins to get into those large electronic medical records, part of the tension is to the extent to which you then are moving away from that; unless you can capture a lot more data and do a lot more complex analysis, looking at phenotypes that are defined electronic in the like, which is possible. But, bottom line is that that's no longer Kidnet. And so, that's part of the challenge. It becomes something else.

And there are activities within FDA, obviously, to try and work in that area, but pediatric is often the tail of the dog and not the dog wagging it. And whether we can get the tail to wag the dog, I guess, is going to be the challenge. Part of asking this question is precisely this tension between this sort of boutique clinical detail, and large databases that you can combine across networks, which is a very different entity; and not something, actually, we in our office would have the expertise to do, frankly.

DR. TURER: The other pieces, you may not need to extract all the data up front. I don't think that would be the most efficient way. I think you identify the signals. And if you retain the identifiable link, rather than extracting the text of an echo, for example, those files are digital, and so, you can actually go back to the studies, and that's critical. So, for the studies that I do, I'll have a pathologist re-read path on slides. And using pathologist who it's their area of expertise. And there are text fields that describe whoever read it the first time, but you can go back to that level of detail when you have a focused question.

I think the first layer is just doing that monitoring. But then, if there's any sort of a signal or concern, you can probe deeper and actually get the primary data.

DR. PEIRIS: I just wanted to add that I haven't had the opportunity to work on the Kidnet project, but just to give a different perspective from devices, because everybody is interested in pediatric devices. Right? Exactly. I thought we were all on the same page.

At the Center for Device and Radiological Health -- I mentioned this last time, as well -- we have a strategic priority for NEST (N-E-S-T) the National Evaluation System for Health Technology. And what we are attempting to create is that infrastructure that will provide information from "every day clinical activities" that will not only help us better refine clinical management for patients, physicians, but also help us from a regulatory standpoint for evaluating our needs on devices.

Certainly, pediatric devices have some unique aspects, but the concepts that have been discussed, so far, in terms of what is the appropriate unique identifier, we have already put forth an opportunity for all manufacturers to be part of the UDI system, the Unique Device Identification System. That is something that each device approved, going forward, will have. That needs to get integrated into the EHR systems and have some method for it to be reimbursed, as we move forward.

The other issue with respect to data security that you mentioned. I think it was very interesting, the comment about having a data secure on a computer that is not attached to the internet. And that is a fantastic option.

The other option, also, is to consider concepts that perhaps maybe -- I don't want to say the next generation -- but perhaps the current generation of how we do data encryption. That data is no longer stored in a single entity. That data for, let's say, one specific topic is dispersed amongst the entire internet, in a sense. Dispersed amongst all iPhones or every other smartphone; and is only reaggregated when specific keys are afforded to the individuals that have those keys to aggregate that information.

But the point being is that in developing the systems, as we move forward, we really need to be very forward-thinking in terms of how technology is advancing. We certainly don't want to iterate on technologies that may be very outdated by the time they are put into place.

DR. WADE: I just had two questions. One, have you thought about how to get a link between a drug exposure and an indication? I know it's something, as we've looked at EMRs before, we can see the drug, we can see the dose, we can see the exposure, but we can't directly link that to an indication. And it seems like, for regulatory work, that might be very important.

And then the second comment -- you can think about it -- is, what's the process by which drugs are prioritized to go through a safety evaluation using an EMR such as Kidnet?

DR. MCMAHON: Okay. Those are great questions. The first question is about indication. Kidnet Number 1, you may have noticed, we got the indications for chylothorax and for hyperinsulinism. So, we went through the charts laboriously and looked for those indications. And it was really a hands-on kind of effort. And I wouldn't recommend it to anyone. It was very difficult, but it did give us some data.

We were able to put our hands on the data about surgical chylothorax and being such high mortality, and hyperinsulinism being lower. But the way we did it was we simply looked through the entire chart. We didn't have any great magical way to get that answer. Because, I agree with you, it's extremely difficult to find in the chart.

It's possible that, in electronic medical records you might be able to find it in a more efficient way; but I haven’t had the opportunity to be able to do that.

DR. WADE: It might just be a question for your Big Data meeting.

DR. MCMAHON: Mm-hmm.

DR. WADE: I think, as we look at some safety exposures where -- some types of EMR data we're less interested in the indication. But for some of the regulatory work, and for some of the reviews that we do, I think we're often interested in what the indication was. And that feels like unless the EMRs request that prescribing physicians link it to something on a diagnosis list, that just has been a challenge. It might be a challenge worth throwing out to the Big Data workshop, that's all.

And the second question was, what is the mechanism by which you prioritize drug evaluation?

DR. MCMAHON: That's a good question. We did the first Kidnet Number 1 because the PAC asked about it, asked about octreotide. I'm not sure about the proton pump inhibitors, Skip. Did they ask about that too, proton pump inhibitors?

DR. NELSON: I don't recall specifically asking. But as you might recall, back around the time PPIs that was before, we all finally accepted the fact that it don't do anything in less than a year age. So, there's a lot of neonatal use. I think the idea was to look at both at the same time.

DR. MCMAHON: Yes. And the second Kidnet was just a direct question, something that we thought would be a little bit easier to get our hands around than the descriptive Kidnet Number 1. And that's also the case with Kidnet Number 3, with renal adverse events and acyclovir use in neonates.

DR. HAVENS: What's the relationship with other groups like the Fizz or Vermont Oxford, or even NIH or other federally funded research networks?

DR. MCMAHON: We did a project -- not as part of Kidnet -- where we outlined what the resources were that were out there. And that was partly for the idea of being able to collaborate with those people, if possible. But we don't have formal relationships with any of those networks as part of Kidnet.

DR. HAVENS: But they have a larger group of hospitals in some situations. Do you have money to bring to get them to buy into your projects?

DR. MCMAHON: I think that's something that we need to consider, but we haven't gone there yet.

DR. HAVENS: So, the sites you use are people willing to do it on their own time, essentially?

DR. MCMAHON: Exactly.

DR. CUNNINGHAM: I'm thinking of personal resource allocation here, but then thinking of other resource allocation, and thinking, for example, of Oxford. Do we know what those other groups are looking into? So, hopefully they're not looking into acyclovir and renal dysfunction, so that we don't repeat what someone else is doing?

DR. MCMAHON: I haven't communicated with investigators of those groups. I obviously looked in the literature, but I haven't communicated with each individual group.

DR. NELSON: And correct me if I'm wrong. The acyclovir question is one that was generated by clinician investigators at one of the sites. So, it was not driven by our question at that point. It was a question they wanted to ask and utilize the resources to ask that question. Is that correct, Ann?

DR. MCMAHON: Yes. And it was discussed within the group, including the FDA group, and thought to be a good use of resources. But it did come, initially, from one of the sites.

DR. NELSON: Right. I'm not suggesting it was a bad question, but it was just that was the nature of the question. And I think, part of the challenge here is, many of the comments people have made is about the importance of large data and, perhaps, even trying to capture information that would allow you to make more nuanced evaluations of that large data. But really, at this point, Kidnet is half a dozen institutions with extraction on either

electronically or by hand going into Redcap, and that's it. So, part of the challenge is asking the types of pediatric safety studies that you could use, using that system, as opposed to let's design another system to do other kinds of studies.

And that's part of the tension around thinking strategically about how to move forward using, if you will, the limited resources available to our office; as opposed to the more vast resources that might be available if we could leverage from a safety perspective, or from other perspectives, what's going on within the FDA, around other kids of databases, which would be an entirely separate set of issues.

DR. TURER: So, I'm not sure these studies would be ready for primetime, and they're not areas in my field at all. But a couple of things that have come out just from my work in academia; one of them being around whether contraceptive use in adolescence could be impacting bone. And that, I say, may not be ready for primetime unless we can follow these children longitudinally into adulthood.

But how this came out, I had a research assistant who had joined the military at 17, had been on depo since she was around 13, and had a hip fracture at 19 in the field. Turns out, military uses Depo-Provera to suppress menses in military personnel. And when I mentioned to her, gosh, that's seems pretty rare. She goes, oh, I had a couple other friends who had hip fractures as well. So, that was very shocking to me. I've talked with people in academia about it, but it seems not something that I can engage people to want to look at. So, that was one study.

And then the other, we had a Harvard faculty member come and give Grand rounds, discussing issues around transgender. And one of the risk factors that was punitive -- I can't remember what the data were based on -- but were around perinatal exposure to progesterone. We use progesterone in pregnant women with threatened pregnancies. And when

I went up and spoke with him afterwards, he said, oh that would never be done in the US, to look at it.

So, it's another thing that I would think maybe the FDA would play a role in looking into some of these things. Maybe even networking with other countries. His response was, you know, I don't think the US is where the studies would be done. I think they would be done elsewhere. Those are two examples that I think would be in the FDA's domain to consider.

DR. HOEHN: My only thought, when you were talking about resources and lack of resources, would be to see if either Cerner or Epic, or one of the companies that have lots of money and lots of technology, would want to do something like that as a project partnering with people. Because I think the vast majority of Children's Hospitals are on one of two systems.

So, if you either got Cerner to do it or got Epic to do it -- because now you can do care everywhere. You can see kids in Epic all different places. There are certainly ways to do that. It would just be a matter of convincing them that it was a good use of their time and money.

DR. JONES: Just thinking about what we could use Kidnet for with how it's now designed. I think a lot of times in these meetings we talk about potential safety signals that we see. Like today, we were talking about the potential safety signal with the CVA in Abilify. Could we use Kidnet to try to follow those questions up and see do we see replication of what we've been presented here at PAC? Or are they stronger or weaker safety signals that would warrant, you know, us going back to the manufacturer and saying, look, we looked at this potential signal in another health system or pediatric hospital, and we think this may be real. Can we do some further look into this? That may be one potential way we can use it how it's currently designed.

DR. NELSON: I think that's a great idea. The challenge is thinking about sample size and the rarity of the event in the extent to which -- I mean I'm reminded -- all of you may remember the LABA discussions and the like. At some point, they'll be some follow-up on what's going on with the studies that have been conducted for safety.

But to look at the signal of hospital admission or death in pediatrics, it required 26,000 patients. So, it's a challenge to think of the sample size you might need to look at some events that might be rare. And the difficulty with the FAERs events is it get reported and you have absolutely no idea what that population is out there to which this little tip of the iceberg has appeared. Maybe you can do that, but you probably could get a negative answer and it might not be the right answer, just based on the size of the sample that you've been able to select from.

DR. JONES: Yes, I agree. There's limitations there. But I also think, with the data that we're presented, most of that data does not come from pediatric hospitals. I think, also there, the signal is probably watered down. At least with Kidnet, it's among pediatric hospitals where these drugs are being used commonly.

DR. HAVENS: But it sounds like the type of study you're allowed to do is based on what the investigators -- this is an ad hoc research network. And so, really what you can do depends on what they want to do with you. Is that fair to say?

DR. MCMAHON: Yes, that's pretty much true. I mean, we're now doing a fourth project, which I'm not going to go into, but basically it's a different subspecialty. So, you have to see whether the subspecialists are interested at these various hospitals. And you can bring in other hospitals, but yes, it really is a lot determined based on subspecialty.

DR. WADE: Well thank you for that presentation, Dr. McMahon. And thank everyone on the PAC for such a vigorous conversation today about all of these devices and products. In a conclusion way, I would say I'm actually grateful that the schedule got altered

and we could end on this discussion of Kidnet. Because I think the one thing we all struggle for, when we get together, is the lack of good data. I applaud the efforts of the workshop in big data.

I think this will get easier, but there are always -- at every committee of the PAC -- is a request for more data, cleaner data, more comprehensive data. I just applaud your effort. I hope that project grows. And, I think, having the workshop with the leaders in big data could really help move it forward.

DR. MCMAHON: Thank you.

DR. WADE: And with that, we will conclude this meeting. Thanks, everyone, safe travels.

[MEETING ADJOURNED]

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