UNITED STATES FOOD AND DRUG ADMINISTRATION

PEDIATRIC ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Tuesday, March 7, 2017

PARTICIPANTS:

Welcome and Introductory Remarks:

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Introduction of New Designated Federal Official and Award Presentation:

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Opening Statement:

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Office of Pediatric Therapeutics
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Center for Biologics Evaluation and Research Presentation

Abbreviated Presentations:

Novoeight Antihemophilic Factor and Rixubis

KENNETH QUINTO, MD, MPH
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PARTICIPANTS (CONT'D):
Initial Post-Market HDE Review:
Epicel

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P R O C E E D I N G S

(8:31 a.m.)

DR. HUDAK: Good morning, we'll get started. This is day two of the Pediatric Advisory Committee meeting. We have a morning agenda that hopefully will proceed a pace. So I think we've got all of the committee members that are likely to be here today. So if everybody has a seat at the table who is going to be at the table we can start with introductions and I think we will start with Dr. Portman. Dr. Portman, we're starting introductions with you.

DR. PORTMAN: Introductions. Yes, I haven't changed since yesterday. I'm still Ron Portman, Pediatric Nephrologist with Novartis Pharmaceuticals.

DR. TURER: Christy Turer, Combined Internal Medicine Pediatrics, UT Southwestern.

DR. SAYEJ: Wael Sayej, Pediatric Gastroenterologist, University of Connecticut.

DR. KASKEL: Rick Kaskel, Pediatric Nephrologist, Albert Einstein Montefiore.

DR. ANNE: Premchand Anne, Pediatric Cardiology, St. John Providence Children's Hospital.

DR. WADE: Kelly Wade, Neonatology, Children's Hospital of Philadelphia and University of Pennsylvania.

DR. CATALETTO: Mary Cataletto, Pediatric Pulmonology, Winthrop University Hospital in New York.

MS. MOORE: Erin Moore, patient advocate.

DR. WHITE: Michael White, Pediatric Cardiologist from the Ochsner Clinical School.

DR. JONES: Bridgette Jones, Allergy and Immunology in Clinical Pharmacology from Children's Mercy Hospital. I'm the healthcare organization representative from the AAP.

DR. CALLAHAN: David Callahan, Child Neurology from Washington University, St. Louis.

DR. BRILL: Marieann Brill, Designated Federal Officer for this meeting.

DR. HUDAK: Mark Hudak, Neonatologist,

University of Florida College of Medicine in Jacksonville.

DR. CNAAN: Avital Cnaan, Biostatistician, George Washington University, D.C.

DR. COPE: Judy Cope, Office of Pediatric Therapeutics, head of the safety team.

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

DR. ZINDERMAN: Craig Zinderman, Division of Epidemiology in the Office of Biostatistics and Epidemiology in CBER.

DR. BAER: Bethany Baer, Medical Officer, CBER Division of Epidemiology.

MS. CHEGE: Wambui Chege, Medical Officer, CBER Division of Epidemiology.

DR. HUDAK: Skip, you have the floor.

DR. NELSON: Thanks. Just a couple of quick comments about the agenda. So we're going to start off with a couple of abbreviated presentations for those that are new to the Committee. These are the style of presentations

that we used to do for the CBER products that are now posted on the web. We're having some discussions with CBER about whether we transition to that process, but to date, have not yet done that. You'll also see a device which is a CBER regulated device and that will be presented by both CDRH and CBER as it transitioned from CDRH to CBER in 2007, somewhere, I have notes. Recently, anyway, it transitioned, I don't have to get the date right. And then we have our annual reviews of the HUD's. Epicel, by the way, is an HUD as well which is why it is coming and for those that are not familiar with the legislation, in an effort to try and stimulate pediatric drug device development, under it was about five years ago now. I don't know if it was under FDASIA or under a separate one. But companies can ask for the ability to earn a profit on the pediatric portion of an HUD and in that same legislation, was put in place, a review by this committee, the law requires us to do that annually. So every year with come back with HUD's that are under that

program of which I think there are about seven or eight at this point. So that is the agenda for today.

DR. HUDAK: Great. I'll turn it over to Marieann.

DR. BRILL: Thank you. Good morning, everyone. The following announcement addresses the issues of conflict of interests 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 federal employees from other agencies that are subject to the Federal Conflict of Interest laws and regulations.

The following information under status of the advisory committee's compliance with the Federal Conflict of Interest laws including but not limited to, 18 USC § 208 of the Federal Food Drug and Cosmetic Act is being provided to participants at this meeting and to the public.

Based on the submitted agenda for the meeting and all financial interests that have been reported by the committee participants, FDA has determined that those individuals who will be participating in each topic are in compliance with federal ethics and conflict of interest laws. In order to provide the expertise required to adequately address all of the products covered at today's meeting, the following expert consultants will be participating as temporary voting members. Dr. Anne, Dr. Kaskel, Dr. Callahan, Dr. Zuppa, Dr. Kishnani and Dr. Peck. Ms. Erin Moore is participating as a patient family representative which is a voting position. Dr. Bridgette Jones, will serve as a pediatric health organization representative which is a non- voting position. Dr. Portman is participating in this meeting as the industry representative acting on behalf of all related industry. He is employed by Novartis Pharmaceuticals Corporation. Dr. Portman, is not a special government employee and does not vote.

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 be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with the firms that could be affected by the committee discussions. I would like to remind the audience that the final version of the agenda and the materials that will be presented at today's meeting will be posted on the Pediatric Advisory Committee website. So any copies of the slides that you have that appear different from the ones that are on the screen will be updated.

For the members of the Committee and those around the table, the meeting is being transcribed and, as such, when you are acknowledged to make a statement or have a

question, please press the button on your microphone and state your name prior to beginning your statement. I also request all meeting attendees to turn their electronic devices to silent mode. Thank you.

DR. HUDAK: Can I ask Dr. Zuppa to introduce herself.

DR. ZUPPA: Hi it is Dr. Zuppa from the Children's Hospital of Philadelphia.

DR. HUDAK: And also, anyone on the phone. Is Dr. Kishnani on the phone?

DR. KISHNANI: Yes, I am on the phone can you hear me?

DR. HUDAK: Yes, very well.

DR. KISHNANI: Thank you, yes.

DR. HUDAK: So today we do not have any registered open public hearing speakers at this time. We're a little early so I'm going to ask Dr. Quinto to do his presentations and we'll come back at about nine o'clock to see if there is anyone here to do open public hearing.

DR. QUINTO: Good morning. I'm

Lieutenant Commander Ken Quinto, Medical Officer in the Office of Pediatric Therapeutics at FDA. I will be presenting the Center for Biologic Evaluation and Research, CBER, products.

The two CBER products presented today will have abbreviated presentations. And just to remind you, CBER abbreviated presentations mean that the forward view was performed. After the forward view, the CBER products met the criteria for an abbreviated presentation format because there are no new safety signals recognized and there are no reports specifically of pediatric deaths that would be attributed to the CBER product. The FDA would see that the products could go back to continued routine monitoring.

The first CBER product is Novoeight Antihemophilic Factor. It is an antihemophilic recombinant Factor VIII product and is indicated for use in adults and children with hemophilia A for the control and prevention of bleeding, perioperative management and routine prophylaxis to prevent or reduce the frequency of bleeding

episodes. The initiation for this pediatric post marketing safety review was the October 15, 2013 initial FDA approval in both adults and children. Based on the background materials you receive; the plan would be that FDA will continue its ongoing standard safety monitoring. Does the Committee concur?

DR. HUDAK: So thank you. So this is open for discussion. So the materials were circulated to all about these two products. Does anybody have any questions for Dr. Quinto? Okay hearing none, we can vote on the recommendation for the FDA to continue its standard safety monitoring on this product and you can vote with your electronic buttons. I will display that on the screen and then we'll do the oral vote and get your vote, Dr. Kishnani. Okay we have the electronic vote which is, so far, unanimous. So we'll start with the oral votes and comments. Dr. Kishnani, do you want to kick it off?

DR. KISHNANI: I agree.

DR. HUDAK: And we'll start this time

with Dr. Cnaan.

DR. CNAAN: I concur.

DR. ZUPPA: Dr. Zuppa, I concur.

DR. CALLAHAN: Dr. Callahan, yes, I concur.

DR. WHITE: Michael White. I didn't register my vote but I concur.

MS. MOORE: Erin Moore, I abstain.

DR. CATALETTO: Mary Cataletto, I concur.

DR. WADE: Kelly Wade, I concur.

DR. ANNE: Dr. Anne, I agree.

DR. KASKEL: Rick Kaskel, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy Turer, I concur.

DR. HUDAK: The Committee is unanimous on the continued routine safety monitoring for this product so Dr. Quinto, Dr. Nelson?

DR. NELSON: Erin you said you abstained, okay, just clarifying, thanks.

DR. QUINTO: The second CBER product is Rixubis. A recombinant coagulation Factor IX

product indicated in adults with hemophilia B for control and prevention of bleeding episodes, perioperative management and routine prophylaxis. The initiation of the pediatric post marketing safety review occurred when the indication was expanded to include use in children on September 12, 2014. Based on the background material you receive the plan would be that FDA will continue its ongoing standard safety monitoring. Does the Committee concur?

DR. HUDAK: Again, this is open for discussion. Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I have a generic question to the FDA. In the previous product, there was utilization data. In this product, utilization data was redacted. What makes one review have utilization data and the next one redacted?

DR. ZINDERMAN: Thanks for the question. So we often ask for utilization data from the sponsor, sometimes the best source to know how much of a product was out there and potentially

used by patients, how much exposure there is is to find out how much of the product was distributed or put into the marketplace over a given time period. So we often go to the sponsor for that data. Under FDA disclosure regulations, we're not permitted to release that data unless we have the permission from the sponsor specifically to release it. There is actually a formal process for them to grant that permission. So in this case, for Rixubis the sponsor did not grant that permission to release that information but it is in the unredacted version of the memo that is provided to the PAC members.

DR. HUDAK: Any other questions? Okay so we will start again on the phone with Dr. Kishnani. Do you concur?

DR. KISHNANI: I concur.

DR. HUDAK: Thank you. Oh, we have to do the electronic. I'm sorry, I got ahead of myself. So everyone else do the electronic voting. So we will go around the room with Dr. Turer first.

DR. TURER: Christy Turer, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. KASKEL: Rick Kaskel, I concur.

DR. ANNE: Premchand Anne, concur.

DR. WADE: Kelly Wade, I concur.

DR. CATALETTO: Mary Cataletto, I concur.

MS. MOORE: Erin Moore, abstain.

DR. WHITE: Michael White, agree.

DR. CALLAHAN: David Callahan, I concur.

DR. ZUPPA: Athena Zuppa, I agree.

DR. CNAAN: Avital Cnaan, I concur.

DR. HUDAK: So for the record we have eleven yeses' and one abstain in favor of this recommendation.

Okay so we are at the position where it is not yet nine o'clock for the open public hearing. And we're trying to see if we can get Dr. Peck on the phone to begin the discussion of Epicel. So I think we have five minutes. We can take a short break until nine o'clock and we'll start with soliciting anyone for open public

hearing. If no one is here, we'll go directly to Epicel.

(Recess)

DR. HUDAK: If everybody could be seated please and stop talking. Okay we have reconvened, it is nine o'clock. This is the time for our open public hearing so we have no registered speakers. Is there anyone in the audience who would like to speak? Seeing no hands and no feet we will move to the next item on the agenda which is a discussion of Epicel. Let me verify that, and Dr. Peck, if you're on the phone, if you could introduce yourself as an expert consultant.

DR. PECK: Yes, good morning everyone. This is Dr. Michael Peck, I'm in Phoenix, Arizona. I am one of the associate directors of the Arizona Burn Center and I've been involved in burn care for about 30 years now.

DR. HUDAK: Excellent, we appreciate your expertise in this and also appreciate your being up at 6 a.m. Arizona time. So we have some other folks from around the table from the FDA if

you could introduce yourselves as well.

DR. ZHU: My name is Yao Yao Zhu, I'm the medical officer from CBER.

DR. MIRSAIDI: Hi, I'm Nasrin Mirsaidi, Division of Post Market Surveillance, Office of Surveillance and Biometrics.

DR. HUDAK: Thank you. And I think at the podium we have Dr. Alimchandani.

DR. ALIMCHANDANI: Yes.

DR. HUDAK: Is that somewhat close to how you pronounce it?

DR. ALIMCHANDANI: Yes.

DR. HUDAK: Thank you and then we'll have Dr. Mirsaidi speaking after you. So we will start the discussion on Epicel, which as you see in your menu, is an HDE, it is a cultured epidermal autograft, thank you.

DR. ALIMCHANDANI: Good morning. We are presenting the Humanitarian Use Device, Epicel. We have two presenters. As we introduced ourselves, my name is Meghna, I'm from the Center for Biologics. My co-presenter is Nasrin from the

Center of Devices.

So this is our presentation outline. Our presentation will focus on the device called Epicel. We will describe this device, highlight key milestones in the regulatory history, summarize preapproval data, present medical device reports, focusing on the pediatric reports, discuss published literature with relevant safety information and end with FDA's recommendations and questions for the PAC.

So Epicel, also known as cultured epidermal autograft, is a wound dressing composed of the patients own autologous keratinocytes that are grown (inaudible). An Epicel graft, has sheets of autologous keratinocytes attached to petrol laden gauze and measures approximately 50 square centimeters. Another thing to note, is that Epicel is a xenotransplantation product. This is because it is manufactured by co-cultivation with proliferation arrested mouse fibroblasts and the grafts have less than one percent

(inaudible) mouse cells. So

Indications for use. Epicel is indicated for use in both adults and children with deep dermal or full thickness burns comprising a total body surface area of 30 percent and greater. Epicel can be used with or without split-thickness autografts.

So this next slide highlights the key milestones in this product's regulatory history. Back in 1988, Genzyme first began marketing Epicel as an unregulated product. In 2007, the Center for Devices approved Epicel as a humanitarian use device. In 2013, Epicel was transferred was transferred from Center for Devices to the Center for Biologics. In 2014, FDA approved a label change to describe the risk of squamous cell carcinoma. We will discuss a label change at length later in the presentation. Also in 2014, there was a change in ownership and Epicel was transferred from Genzyme to Vericel Corporation. So last year, in 2016, FDA approved pediatric labeling for this product which is the trigger for

the PAC presentation today.

Preapproval data for safety and probable benefit come from two sources. Number one, the Genzyme biosurgery Epicel clinical experience and number two, the Munster study. Genzyme surveillance database covered the period from 1989 to 2006. And as you can see from these numbers, the database included data on more than 1300 patients who were treated with Epicel prior to approval. The survival rates were 86 percent to 91 percent. The Munster study was published in 1996 and was an independent physician sponsored study conducted by Dr. Munster at Johns Hopkins Burn Center. This was a prospective control style that compared the outcome of therapy in burn patients treated with or without Epicel. Genzyme collected data from the medical records of 44 patients in this study and the survival rate, as you can see, was 90 percent in the Epicel group and 37 percent in the control in the group.

So this slide lists the adverse events following Epicel and include the following:

death, sepsis, infection, multiorgan failure, graft sharing, debridement, detachment, et cetera. These adverse events are typical of those seen with severe burn injuries and skin grafting procedures. Based on the preapproval data, the Center for Devices decided that Epicel met the requirements of relative safety and probable benefit in the treatment of large TBSA burns. And Epicel was approved as a humanitarian use device in 2007.

So although children had been treated with Epicel there was no specific pediatric labeling. Since 2007 approval, 30 percent of Epicel recipients are children. Last year, in February 2016, FDA approved pediatric labeling and the annual distribution number. I'm going to describe the ADN on the next slide. The revised label displays separate safety and probable benefit data for children and adults.

So the Food, Drug and Cosmetic Act allows HDE's indicated for pediatric use to be sold for profit as long as the number of

distributed devices does not exceed the annual distribution number. The currently approved ADN is 360,400 Epicel grafts. This is based on an average 90 grafts used per patient multiplied by 4000 patients which was the target population as per HDE definition at the time of the February 2016 approval. I want to take a moment here, and note, that as per the recent 21st Century Cures Act, the HDE definition of the target population has now been revised to be 8000 patients. Epicel sales have not exceeded the ADN.

So now, I'm going to hand it over to Nasrin, from the Center for Devices, who will present the medical device report analysis.

DR. MIRSAIDI: Hi everyone. My name is Nasrin Mirsaidi. I'm the MDR analyst at the Division of Post Market Surveillance, Office of Surveillance and Biometrics. I will be presenting MDR analysis related to Epicel with my focus primarily on pediatric patients. I will begin with a brief description of medical device reporting system and its limitations and then I

will describe the database search that we did to capture all the MDRs related to Epicel and then provide the summary of findings and analysis of the reports.

This slide shows the limitations of MDR data. Each year, FDA receives over one million MDRs and reporting suspected device associated deaths, serious injuries and malfunctions. FDA uses MDRs to monitor post market device performance, detect potential device related safety issues and contribute to benefit risk assessment of devices. Although MDRs are a valuable source of information and this passive surveillance system has its own limitation and has you see in this slide, we have under reporting.

We believe what we receive through MDRs is just a subset of all the occurrences out there. The quality of the MDRs are not that great. Sometimes we receive incomplete, inaccurate, sometimes unverified and biased data. We cannot infer cause and effects relationship from individuals report especially when the

circumstances surrounding the event is not verified or the device involved is not directly evaluated. In addition to incomplete numerator, we do not receive denominator data through MDR, therefore we cannot determine accurate incidence rate because of under reporting and lack of denominator.

Our database called System for Uniform Surveillance houses MDRs as submitted to FDA by mandatory reporters such as manufacturers, user facilities, importers as well as voluntary reporters such as health professionals, patients and consumers. For the purpose of this analysis, I searched the database with the search criteria of brand name of the device which was Epicel with no date restrictions so we could capture all existing MDRs in the database. So with this search criteria we identified 90 MDRs.

As you will see this graft here shows the MDRs received by year. The graft was too large for this slide so it is shrunken and you cannot see every single year. We just did 90

reports since 2000 and all the MDRs were submitted by manufacturers, 84 of them by Genzyme Biosurgery, 6 of them by Vericel Corporation.

The red columns are representative of pediatric patients and the blue column is representative of adult patients. As you see there is a peak in 2008 which we are not quite clear about this but we are guessing it might be related to the approval of Epicel for HDE in 2007. Also, there is a gap in 2009. Actually, there was a report that the date of event was 2009 but we did not see it until 2011 so that report is in the 2011 receipt of MDRs.

Now the type of event for the 2009 patients that include both pediatric and adult patients there were 76 deaths, 12 injuries and 2 malfunctions. MDR reported several clinical issues, patient problems and complications for each patient. But the most reported adverse event that might be potentially related to the death of the patient is multi organ failure with 38 patients, 42.2 percent of the population. Sepsis

was the second most reported adverse events with 28 reports which was 31 percent of the 90 MDRs. The third most reported adverse event was cardiac problems such as cardiac arrest, cardiogenic shock, cardiopulmonary failure with 11 patients which was 12 percent of the 90 patients.

From this point, I will focus on pediatric patients. Twenty of these patients were pediatric patients and the age for the pediatric patients ranged from 2 years to 21 years with mean age of 13.4. Eight patients actually were under 10 years, 6 of them between 10 and 20 years and 6 between 20 and 21. Six of the 20 patients were female and 14 were male. The total body surface area of burn was reported only in 14 patients and in those 14 patients it was between 35 percent and 99 percent, mean of 85 percent and median of 91.5.

Focusing on pediatric patient death we had 15 deaths in pediatric patients. Again, there were multiple clinical issues that was reported in the reports but the most reported adverse event that might have caused the patient death was multi

organ failure in a number of which sepsis and infection was the underlying cause. Other adverse events were one patient died of squamous cell carcinoma, one patient of cardiac arrest, one patient focal dermal hypoplasia, also known as Gold Syndrome, in which the Epicel was used as off-label. One patient died of mixed drug interaction and was not related to the Epicel and one patient it just said that the patient died of complications of full thickness burn, so no details about other complications.

Pediatric injury and malfunction reports. There were four injury reports and those four included three infection and one patient had to have a foot amputation with no details about why and how. But after getting the Epicel graft he required foot amputation. There was only one in the last 20 reports that was reported as malfunction in this report. One of the lot numbers of the grafts after the patient received the graft was confirmed to be contaminated. And the company contacted the physician, followed up

with the physician, informed them that the graft was contaminated but as far as they know, the patient did not have any complications, so it was submitted as malfunction.

Now summary of MDRs. We received 90 reports from 2000, 20 of them were pediatric patients. Pediatric patients had 15 deaths, 4 injuries and 1 malfunction. Most reported adverse event was multiorgan failure both in pediatric and adult patients. The mean TBSA was 85 percent in pediatric patients.

DR. ALIMCHANDANI: Thank you, Nasrin. Now we will go over the literature review results. (Inaudible) using the tech strings that are listed here. There were 32 articles published in the post-market period which were reviewed for relevant safety information. There was one literature case report of graft site malignancy which I will describe on the next slide. No new safety issues were identified from review of the remaining articles.

So this is a case report of graft site

malignancy involving squamous cell carcinoma. A 34 year old man with 95 percent TBSA burns was grafted with Epicel, 13.5 years after grafting, he developed squamous cell cancer. What was striking about this case was the multicentric presentation and recurrent lesions. He developed SCC at five graft sites which was described in a previous publication. The 2015 publication sited here provides long term follow up on the same patient who went on to develop eight additional SCC lesions. The patients survived and is closely monitored. As mentioned previously, the label was revised in 2014 to describe the risk of squamous cell cancer and we will discuss this in greater detail on the next few slides.

So there are six reports of squamous cell carcinoma after Epicel use. But before I go over the cases described in this table, I want to point out that an estimated two percent of burn scars undergo malignant transformation and squamous cell cancer is the most common skin cancer to develop from burn scars. That being

said, there are certain distinctive features about the cases that are described in this table.

The first case, as you can see, dates back to preapproval data and involves off-label use in a dystrophic epidermolysis bullosa patient. DEB, is a genetic disorder characterized by chronic open wounds and non-healing ulcers. And importantly, DEB patients have an increased risk of squamous cell cancer. This patient develops squamous cell cancer a few days following Epicel grafting in 1994 and needed below the knee amputation. Of note, this case is described in the current label.

The second case, is a literature case report that we just went over in the previous slide. The 34 year old man who developed multiple SCC lesions and survived.

The third case, is a med watch report of a pediatric death. An 8 year old child with 99 percent TBSA burns was grafted with Epicel. About 12 years later, he developed multiple squamous cell carcinoma lesions in the abdomen, knee and

foot. His tumor had aggressive features and he died. This case is also described in the current label.

The fourth and the fifth cases were submitted by the same reported and involved patients of unknown age, unknown burn sites. One patient developed squamous cell cancer 15 years after grafting and survived, and the other patient developed squamous cell cancer 19 years after grafting and died.

The sixth case involved a 46 year old man with 95 percent burns who developed SCC 13 years after grafting and survived.

So I wanted to point out the distinctive features in some of the Epicel cases. Firstly, the episode graft sites, squamous cell carcinomas developed with shorter latency periods as compared to a latency period of more than 30 years for squamous cell cancer to develop and burn scars not treated with Epicel. Some of the Epicel cases had aggressive features such as multicentric growth, large size, local recurrence and there were fatal

outcomes including one pediatric death.

On the next slides, we will show you the label change. So as I mentioned several times in 2014, FDA approved revisions to the Epicel label. The revisions included three documents. The directions for use warning section, patient information document and a dear healthcare provider letter was issued by the manufacturer in June 2014.

There is a lot of text on this slide. This is excerpted verbatim from the current label from the directions for use warning section and there were just a couple of things I wanted to point out. So as you can see, the distinctive features of the Epicel cases such as multicentric location, large size, aggressive growth, local recurrence, fatal outcomes have been described in the label along with the shorter latency periods. And you can also see that the pediatric death is described in detail in the label. The label states that although squamous cell cancer is a known complication of burn scars in DEB, the role

of Epicel and the causation of SCC cannot be excluded.

So as we have described, Epicel is an autologous product and Epicel is also a tracked medical device. And on this slide, we wanted to present tracking data that is available in the current label in the directions for use. The tracking data is collected by the manufacturer and includes survival data. In the post-market period, 2007 through 2015, there were 120 children who were grafted with Epicel and the survival rate was 88 percent. Overall, there were 402 adults and children treated with Epicel and the overall survival rate was 81 percent.

FDA inclusions are presented on this slide. We have described the 2014 label revision to include the risk for squamous cell cancer. From the medical device report analysis presented earlier by Nasrin, we can see that adverse events in children and adults were consistent with the complications of severe burn injuries such as sepsis and multiorgan failure. Also keep in mind,

that there is a high rate of mortality in the indicated patient population with severe burn injuries. Recent U.S. data showed that more than 65 percent TBSA burns are associated with 50 percent case fatality. And as you have seen from the MDR data episode treated patients had severe burn injuries. In pediatric medical device reports, comprising 20 (25%) of the reports. The average pediatric TBSA was 85%. So in conclusion, FDA did not identify any new safety signals. FDA will continue surveillance and will provide an annual update to the PAC in 2018. This presentation and executive summary for Epicel was put together by both the Center for Biologics and the Center for Devices. We thank the many people involved from both the centers and multiple offices. So we end with our question to the PAC, does the Committee agree with FDA's conclusions and recommendation.

DR. HUDAK: Okay we have another FDA guest at the table. Would you introduce yourself.

DR. PARIS: Vasum Peiris, I'm the Chief

Medical Officer for Pediatrics and Special Populations with the Center for Devices and Radiological Health.

DR. HUDAK: Thank you. So this is, maybe we can put the slide up about the conclusions and recommendations. Thank you. Perhaps before we get started around the table, I'll give Dr. Peck a chance to comment since he has had long experience with this product. Dr. Peck.

DR. PECK: Thank you very much. Can everybody hear me?

DR. HUDAK: Yes, you're very clear.

DR. PECK: Okay, excellent. Let me speak briefly to this just trying to put this issue into perspective. The size of the burn injury which is described as the percentage of the body's surface area is a marker of the severity of injury. And what we know is that once the burn size has gone beyond 20 percent of the body surface area there is an impairment of the immune system and an inability to deal appropriately with

bacterial and fungal infections.

In addition, there is an increased risk of multiple organ system failure, probably because of impairments of the immune system. At any rate, everything that you're seeing here is very consistent with outcomes that we know occur with large burn injuries. You're talking about a median burn size of 92 percent. Even in otherwise healthy children, the risk of mortality is going to be very high because of the burn injury.

The product itself is the attempt on the part of the clinician to resolve the injury challenge to the patient. The problem is, that the immune system remains impaired until the wound is closed. So the goal is to try to close the wounds as quickly as possible.

Epicel is one of the approaches that are used out there for closing wounds. It is unique in the sense that it is the only cultured product that is permanent. That is to say, there are

other products that you can pull off the shelf. A good example is Integra. Some people call it artificial skin. Integra can be laid onto an open wound but it is not a permanent solution. You still have to take the patients skin and cover it.

So Epicel is truly unique, in that it is the only product that we have available to us that provides permanent coverage of the patients own skin. Having said that, it is not perfect and I think all of us were concerned in 2014 when these reports of squamous cell carcinoma came up. But as already has been pointed out, squamous cell carcinoma is not uncommon in patients who are recovering from burn injuries. It is true that the literature says that there is typically a

year lag period for development but there is a huge range in there.

I will say that I don't think that we, in my field, have done a very good job of documenting everything we know about squamous cell carcinoma. In our unit alone, just in the last six months, we've seen three patients who have

developed squamous cell carcinoma in their wounds within a six to eight month period of time after injury. So development sooner than years is not unusual and the presentation times that have been presented today are not surprising to me. It is entirely possible that these cases of squamous cell carcinoma might have arisen in these patients even if they would have been covered with some other method.

Nonetheless, I think that the changes in labeling, the increased alertness to the concern about the squamous cell carcinoma enables us and probably gives us, the clinicians, the responsibility to communicate this to the parents of these patients before we utilize these products. But the truth of it is that you're talking about the difference between a slightly increased risk of squamous cell carcinoma several years from now, a condition that often times is easily managed versus a life threatening condition in the intensive care unit where the only alternative you may have for wound closure is

using CEA. So I agree with the FDA recommendation and I would be glad to answer any questions.

DR. HUDAK: Thank you. That is a very good and relevant clinical summary. We'll start with any questions from members around the table. Yes, Dr. Jones.

DR. JONES: I was wondering, do you guys have any information or maybe the speaker on the phone has any information regarding the mortality rate from squamous cell carcinoma in patients that receive Epicel compared to patients that receive other types of autologous skin grafts or other types of skin grafts. Because it seems like the squamous cell carcinoma in the patients described seem very aggressive. So do you typically see that type of aggressive squamous cell carcinoma in other patients?

DR. PECK: Would you like for me to answer? I'd be glad to answer that. I think that the typical squamous cell that we see arising in burns scars is a relatively benign condition that can be typically treated with local surgical

excision. It rarely metastasizes. Radiotherapy is rarely required for management of these problems so I would agree at least on the surface, it appears that the squamous cell that arises after episode use may be more aggressive but I don't know that there is any literature that specifically addresses that.

DR. HUDAK: Dr. Zuppa.

DR. ZUPPA: Hi it is Athena Zuppa. I want to say thank you to the person on the phone, I don't know the name. I think one of my first questions, I have a couple of questions. So mortality. So I think we always struggle with outcome metrics for interventions and it seems sometimes mortality is not the best outcome metric because the incidents of death is so low. But it seems that the incidents of death in this population is high enough that it can be used as an outcome metric. Number one, I'm curious as to why that was chosen as such an important outcome metric for this population when we're doing something to the skin. I guess it would translate

down to improvement in immune system, improvement in modes, improvement in overall survival. So that is my first question. I'm trying to get a sense from the room why if people think mortality is the appropriate end point for this intervention.

DR. PECK: That is an interesting question. Clearly if you have a patient, pediatric or adult, that has an 85 or

percent burn, if the clinicians don't cover the wounds with something, that patient will die for sure. So what you are looking at then is comparing Epicel to other alternatives out there such as just widely meshed skin graft for example. I am almost positive based on my familiarity with the literature, there haven't been any randomized prospective controlled trials done of Epicel comparing it to widely meshed split thickness autograft in patients with large burn injuries. So we don't have that information but I agree, that I think mortality in this population is a very appropriate outcome measure to follow because it is very highly elevated and effective and

satisfactory wound coverage will make the difference between survival and mortality in these patients.

DR. ZUPPA: So then I think my follow up question would be, and you alluded to it, is whether or not information on mortality and death in patients that were treated with Epicel versus alternative strategies would be informative for us to make an assessment of its safety. Number two, what they landscape of squamous cell carcinoma in patients not treated with Epicel looks like. So the severity, the incidents versus those that are not and burn patients, whether or not having that -- we spoke yesterday about the need for a control group. I don't think that was presented today but I wonder if that would be informative to make these safety decisions.

DR. PECK: I don't disagree at all. I think that would be extremely important information to have for a variety of reasons. There are problems with obtaining those data. Such studies would be, well it would require the

participation of many sensors across the country. The reality is, and this is a good thing, the epidemiology is that the incidents of large burn injuries in children in the United States is decreasing over time. So that is great except that if you try to do a study like this what it means is that a study could drag on for years and it would be very expensive to run. So in my specialty, we don't hold out any hope that such a study will ever be performed. Although clearly, the information from it would be extremely important.

As far as your question about the severity of squamous cell carcinoma in these patients I think that that on the other hand could be handled effectively with the development of a registry. A registry in which patients both adult and pediatric who are treated with Epicel are followed over a period of time and information related to the development of squamous cell carcinoma and the characteristics of the severity of the squamous cell when it does develop could be

gathered into that registry.

DR. HUDAK: Dr. Zuppa has one more question.

DR. ZUPPA: I'm not promising one more. I'm sorry to monopolize. So early in the presentation we heard that patients that had large body surface area burns were not necessarily candidates for this approach because you to use the own individuals skin. But yet we're hearing that the mean body surface area burn is 85 percent which means that there are kids that had greater than 85 percent of their body surface area burned. That is a lot, in my opinion, so I'm just trying figure what the cutoff is for a percent body surface area to be a candidate for this treatment.

And then I also wonder if there is some type of, I guess, I'm not a statistician but selection bias if we're looking at this. So it would seem that the kids that are getting Epicel based on what was initially presented that it is those that don't have large body surface area burns might be a less sick group. So it was kind

of contradictory in saying that the mean is 85 percent. I don't know if I'm being clear on my question so I'll clarify if I need to. Anybody?

DR. ALIMCHANDANI: So I'll try to answer that question. The Epicel recipients are patients with large TBSA burns. They are not candidates for split-thickness autografts but they are candidates for Epicel because all you need is one skin biopsy and then you'll growing expanding the cells exuvial does that make sense? Okay so this is a very sick patient population. The indication is 30 percent and greater TBSA but the mean TBSA that we see in at least in the medical device reports is more than 85 percent for the pediatric patients. Does that answer question?

DR. ZUPPA: It does, I misunderstood what was said. Thank you.

DR. ALIMCHANDANI: Thanks.

DR. HUDAK: Any other questions around the table? Dr. Jones.

DR. JONES: Bridgette Jones. So along the lines of discussing a registry you mentioned

that Epicel is a tracked medical device so FDA will collect data on demographics and survival information for the device. Does that include other outcomes such as the squamous cell carcinoma and whether it is multifocal carcinoma that would allow us to make more informed decisions about this later?

DR. ZINDERMAN: The tracking requirements only include what it says there to maintain the demographic information and that is really for the purpose of contacting a patient should there be a problem in the future with the products or suspicion of infection or something. They don't routinely collect adverse event information in follow up as part of that tracking, although, I understand, if the sponsor company does contact a patient or family and learns some information then obviously they would have that information and would report it if it qualified for an MDR report but it is not a routine part of the tracking.

DR. JONES: Is the tracking done by the

sponsor?

DR. ZINDERMAN: Yes the tracking is done by the sponsor.

DR. JONES: Okay so I think a registry is a great idea especially for the pediatric patients to follow them and collect more detailed information about the outcomes they're experiencing. Especially focusing on the squamous cell carcinoma and how aggressive it is and whether it is multifocal or non-multifocal so that we can use that data and compare that to other children that have not received the same type of grafting. So I think could potentially be a recommendation to the sponsor.

DR. HUDAK: Dr. White.

DR. WHITE: If I might, once again, put in a plug. This is an HDE and the requirements for approval of an HDE are safety and probable benefit. One of the advantages of an HDE currently is in children, they can charge and make a profit on the use of these devices. One of the problems is, they are approved on the basis of

probable benefit and we don't have a mechanism for tracking in these devices. I would really love to see some sort of change in the way HDEs are granted that the tracking does include data going forward for benefit. That is must my five cents worth.

DR. HUDAK: I don't if someone from the FDA wants to comment on the two questions from the two panelists.

DR. NELSON: Let me try to help. The point about the HDE process, it would be wonderful to have more accurate tracking of all devices in all areas with much more clear information. I think our regular presentations here help you to understand the deficiencies that we have with respect to the current MDR process. That is not necessarily to say that the process is ineffective for its purpose but there are ways that a more optimal tracking system overall could be developed. That also has great cost and great resource necessities. So aside from the benefits from a clinical perspective to actually have this

data perfect it is difficult to create the sustainable systems that can help us and continue to collect that data.

The being said, going back to the registry concept, registries also have a resource cost to them. The issue is how can most effectively develop registries that assist for the needs for all stakeholders. The purpose of the registry that has been discussed here is specifically understand the squamous cell carcinoma issues and potentially from the comments earlier, to understand the variable severity of the population that is actually being treated with Epicel versus others.

At the FDA, at least with these devices, we're not necessarily attempting to address comparative effectiveness, so I want to clarify that. The information that is being presented to you from the MDR reports, in a sense, do present a potentially more severe picture. However, those are the major reports that we expect to receive from an MDR reporting system. We don't have the

baseline data of how often this is utilized without any significant issues going on as well. If there are any further questions I'd be happy to clarify.

DR. HUDAK: Thank you. Dr. Turer.

DR. TURER: Christy Turer. One thing that really struck me was reading the Munster study for two reasons. First, it was, the data really suggests a mortality benefit. On the other hand, it was conducted in 1996 and it seems to be a stand-alone study without any follow up. If one were to compare a drug trial in which somebody did a single site study with the few patients that they did and used that as a basis for your risk benefit analysis, people would go, whoa, wait a minute. So I think the standards of care in burn patients have changed significantly over the past 20 years and I do think it would bear coming back to understand what is the current state of mortality related to burns stratified by how much surface area is affected.

DR. HUDAK: So perhaps, Dr. Peck, maybe

you can comment and illuminate us on this. In terms of pediatric patients with TBSA's greater than 30 percent who are eligible for Epicel, what is the percent of these patients in which Epicel is used and how might that be stratified by TBSA.

DR. PECK: Well that is a great question. The use of Epicel at this point in time is dependent upon the experience and preferences of a clinician that is treating the patient. Quite honestly, not everybody is in love with Epicel. It is very sensitive to bacterial colonization of the wound and it is very easy to lose these grafts. And then when the wounds do heal, they tend to heal with a fairly significant amount of hypertrophic scarring. It is not a perfect product. Some people feel that it is the best option.

Many of us combine it with other modalities for wound closure. For example, what we do is we will take the patient's own skin, take a split-thickness graft. We'll mesh it widely, for example, four to one expansion and we'll apply

the meshed skin graft to the wound and then we'll lay Epicel over that as an attempt to help the interstices and the meshed graft heal more quickly. We don't usually use it as a stand-alone product. Some people do.

So there is a great deal of variation out there and the application of the use for this product and consequently a great deal of variation in the indications that clinicians have for using it. Some people would not use it unless there clearly was no hope of using the patient's own donor sites as a source of grafting material. So when you talk about patients with 85 percent, 90 percent of the body surface area burned, you're often talking about patients who don't have any usable donor sites. Maybe the only areas that aren't burned are places like the soles of the feet or the groin or the face, places where you really can't harvest skin from so you're left without any options for skin closure except to go to Epicel.

On the other hand, as we saw a few

minutes ago, at the lower range of the spectrum, you have patients with burns as low as 35 percent who are being treated. Clearly, at least in my mind, that suggests that that was done at an institution where there were clinicians who were very comfortable with the use of Epicel who had confidence in it and who believed that the outcome they achieved with it was satisfactory. Therefore, they felt that it was preferable to use Epicel rather than to harvest the patient's donor sites and use his or her own skin.

So I think that you can say I think without question that when you start talking about patients with burns more than 50 or 60 percent of the body surface area, that you're talking about patients with limited donor sites who would be excellent candidates for Epicel. Then when you get up into the 80 to 90 percent range, you're talking about patients for whom, perhaps, the only alternative for wound coverage is Epicel. Although 50 percent, I think that it is up to the clinicians to decide that whether the results if

they believed is ill obtained from using the Epicel such as with the sandwich technique that I described, are going to be preferable to not using the Epicel.

I don't know if that helps any. I tell you, there is not a lot of science to this field. We do not know as much as we need to know or should know about wound coverage in these patients.

DR. HUDAK: Thank you that was helpful. Dr. Nelson.

DR. ALIMCHANDANI: Just to add one more comment about the recent data. So the 2016 National Bone Repository data that I showed on slide 25 that says that 50 percent case fatality for more than 65 percent TBSA burns. So this is pretty recent data. It was a ten year period from 2006 to 2015 that the numbers were based on.

DR. NELSON: Just a couple of quick comments. I think it is important to keep in mind, the standard for approving a humanitarian use device of probable benefit which is a very

different standard than either approval of devices outside of humanitarian use or for the drug approvals. And I don't think anyone would doubt that covering a burn with something is a probable benefit and the Munster study demonstrated that.

It is an interesting question whether standards of care would change so quickly that, in fact, you would no longer have probable benefit but I doubt in the case of burns of the severity that have been mentioned at that level, that that would be the case. You still need coverage and from what I'm hearing there is a lot of clinician variability. And so part of what also needs to be factored in here is the sort of clinician decision making which in many ways parallels the use of drugs as well. There is a lot of variability separate from how things might be labeled and whether or not someone would only use it in individuals who have no other sites to harvest sounds like it would be a clinical decision making.

I won't mention the product because you

haven't been cleared but prior to joining FDA, I was on a panel and asked to vote on whether something should be approved as an HUD and that was I think, twelve patients. There was a lot of controversy, the decision was finally yes, but it was the size of those kinds of studies are quite small and I frankly was struck by the robustness of this in the humanitarian use device domain which is a very different domain then drug approvals or even standard device approval.

DR. HUDAK: Any other comments? So before we bring up the slide for the question on the recommendation on this, I think I can summarize, I think it is the sense of the Committee that this appears to be -- well first of all, it is not the purpose of the Committee to comment on the decision to grant an HDE. We're purely looking at the FDA recommendation there. But it is the Committee that there could be additional information developed about the squamous cell carcinoma question. We recognize the FDA doesn't have any regulatory power to

compel that to happen but certainly there is a persuasive element to what the FDA can do in this regard and perhaps that might be something that is communicated with the sponsor of the HDE. Anybody else have comments.

If not, we will vote on the FDA recommendation on the screen which is to continue to the surveillance and report back in 2008 to us about the distribution use and the results of the MDR literature review on Epicel safety and survival issues. So we'll vote electronically. Dr. Peck and Dr. Kishnani, we'll pick you up orally at the end of that. Dr. Nelson.

DR. NELSON: Just while people are voting, I would like to ask a question. After the vote, make sure Dr. Peck doesn't hang up too quickly.

DR. PECK: I heard that, thank you.

DR. HUDAK: I just want to make sure everybody had a chance to electronically vote who will. Okay we'll do the oral voting. We'll start on the phone. Dr. Kishnani first.

DR. KISHNANI: I concur.

DR. HUDAK: Dr. Peck.

DR. PECK: I concur.

DR. HUDAK: And we'll go around the table starting with Dr. Turer.

DR. TURER: I concur and it sounds like if the mortality rate is now 65 percent that that has improved from the 37.5 percent in the Munster study and still below the rate of survival in the current data with Epicel at 88 percent. So, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. KASKEL: Rick Kaskel, I concur.

DR. ANNE: Dr. Anne, I concur.

DR. WADE: Kelly Wade, I concur.

DR. CATALETTO: Mary Cataletto, I concur.

MS. MOORE: Erin Moore, I agree.

DR. WHITE: Michael White, I agree.

DR. CALLAHAN: David Callahan, I agree.

DR. ZUPPA: Athena Zuppa, I agree but I just would like to also say if possible, it would

be great to also have information on patients who received Epicel and did not have adverse events and patients who are not receiving Epicel, thanks.

DR. CNAAN: Avital Cnaan, I concur.

DR. HUDAK: Okay that is a unanimous endorsement of continued monitoring of Epicel. And Dr. Nelson, you have a question for Dr. Peck.

DR. NELSON: It somewhat builds on what Athena Zuppa mentioned because I gathered from your comment, Dr. Peck, about recently having seen squamous cell carcinoma, for example, within eight months et cetera. Part of the problem is even if FDA could explore and perhaps did have the authority to ask the sponsor to track adverse events or squamous cell carcinoma in those who received Epicel, really the difficulty there is understanding that relative to a comparator which would be those who had a similar severity of burns and received other products or other mechanisms but also Epicel didn't develop that. From your comment, I gather you're skeptical, at least in this point in time, about the sort of reporting in

the literature and the like of squamous cell carcinoma across burn centers. And so to try and get a handle on that sounds like would be a much larger question then simply asking the sponsor to track squamous cell carcinoma in Epicel recipients. Is that a fair interpretation of your remark?

DR. PECK: So if I understand the question, what I'm hearing is how challenging would it be to gather all of the epidemiological information that we need about the development of squamous cell carcinoma in scars. Is that correct?

DR. NELSON: That is a nice summary of my longer question.

DR. PECK: Well, I tell you, I think it would be very difficult because many of these patients end up going to other practitioners to be seen for the problems that develop. So you can imagine, it is now 15, 20 years after somebody has been burned. They may have moved out of town. They now have breakdown in their skin. They go to

a dermatologist. The dermatologist does the biopsy, creates the treatment plan for them, they're never again seen by a burn doctor for this problem. So the person who applied the Epicel is no longer in contact with the patient. The institution that applied the Epicel no longer has contact with the person. You would have to depend entirely on the willingness of the patients who had had the Epicel applied to them to provide that follow up information. I don't know that much about this field but it seems to me that that would an almost impossible task.

DR. NELSON: Well as a follow up, I'm assuming that part of the tracking here is because it is xenograft which is a fairly standard tracking. So it is possible that individuals who receive it might be motivated. Part of the difficulty is it sounds like the comparator group. It would be unclear how you would interpret those data from your comments about the experience in those who have not received Epicel. So I'm asking as much about the complexity of the comparator

which sounds like it would be even more difficult.

DR. PECK: I agree with you. The American Burn Association which is our National Medical Association for burn care providers does maintain a national burn repository in Chicago which tracks information primarily on the acute care of burn patients typically after patients have recovered a year from their injuries, they tend to fall out of the system. So we have no long term way of tracking that comparator group that you're talking about. There would have to be a mechanism established for doing that.

DR. HUDAK: Okay I think that it still would be valuable to have information even if there isn't a comparator group just for natural history and counseling purposes for these patients. So recognizing that it is difficult, whatever information can be complied would be helpful.

DR. PEIRIS: Can I add one quick comment to this discussion?

DR. HUDAK: Sure.

DR. PEIRIS: This is just a little bit more of a global topic. But since this is a concern and an issue that comes up regularly during the PAC meetings with respect to the information and data that we have for tracking these devices. And truly beginning to understand potential comparative effectiveness issues and also beginning to understand whether these devices are making a significant potential benefit to patients. I want to let everybody know that CDRH is currently in process in developing what we call NESHT, the National Evaluation System for Health Technologies. The intent here is to develop a much more robust system both for understanding products once they're on the market and being able to have information about those products that are relevant to all stakeholders including industry, FDA regulators and clinicians. So systems like this, the concept of systems like this are partly what we are discussing here. So that process is going forward.

DR. HUDAK: Thank you, good to know and

we welcome that. So let me just sort of do a quick sort of roll call here. Our next item on the agenda is the review of the Medtronic Activa. Do we have all of the FDA people here who - - oh, Dr. Peck, thank you very much. We've come to the conclusion for the part of the meeting for which you were mandatorily invited. You're free to hang up.

DR. PECK: Thank you very much for the opportunity to speak with you today about this product and I greatly appreciate all of the time and effort that you all are putting into it. Thank you and have a very nice day.

DR. HUDAK: Thank you, bye now. So Medtronic, do we have FDA staff here prepared? So we'll see how the morning goes and see how efficient these presentations are to see if we can motor through the remaining three or whether we'll have to take a break at some point. One other announcement here is the CDs that you received, Pam will be collecting those so be sure you turn those into her before the end of the meeting.

That would be good. So who is coming to the podium Dr. Miller? No, Mr. Miller, sorry.

All right let's start with having the FDA staff here at the table introduce yourselves for us and then Mr. Miller.

MR. MARJENIN: Hi my name is Timothy Marjenin, I'm the Chief of the Neurostimulation Devices Neurology branch in the Office of Device Evaluation in CDRH.

MS. MILLIN: Hello I'm Courtney Millin. I'm an adverse evdent analyst with the neurology devices within CDRH.

MS. BAYDOUN: Hi my name is Hind Bajdoun. I'm an epidemiologist in the Division of Epidemiology at CDRH.

MR. MILLER: Good morning, I'm Andrew Miller and I'm MDR analyst in the Office of Surveillance and Biometrics within the Center for Devices and Radiological Health. I'll be presenting the annual safety update on the use of the Medtronic Activa Neurostimulator for treatment of dystonia in pediatric patients. This is the

fourth time this device has been reviewed by the panel.

The Activa system consists of three main components including a Neurostimulator, extension and lead. The implanted Neurostimulator is the power source for the system. This small pacemaker like device contains a battery and its programed to send electrical signals to manage dystonia symptoms.

The extension is an insulated wire placed between the scalp and the skull that connects to the lead and runs behind the ear, down the neck and into the chest below the collarbone where it connects to the neurostimulator. The lead is a set of thin wires covered with a protective coating that carries the stimulation signal to the electrodes that deliver the signal to the brain. Part of the lead is implanted inside of the brain; the rest of the lead is implanted under the skin of the scalp.

The Activa Neurostimulator was originally approved for the treatment of

Parkinsonian tremor in 1997 and subsequently received HDE approval in 2003 for the treatment of dystonia in adults and pediatric patients, seven years of age or older. The specific dystonia indications for use are provided on this slide.

The HDE was approved with an annual distribution number of 4000 devices. A total of 836 devices were implanted in 2016, 139 of which were implanted in pediatric patients. There were 3440 active implants in 2016 including 581 active pediatric implants.

Many or most of you are likely familiar with CDRH adverse event reports or MDRs. This slide provides a brief reminder of the limitations of MDR data. Although MDRs are a valuable source of information, this passive surveillance system has limitations including under reporting and data quality issues. Additionally, the incidents or prevalence of an event cannot be determined from MDRs alone due to potential under reporting of events and lack of information about frequency of device use. Finally, it is not possible to

definitively determine a causal relationship between an event and the device based on MDR data alone.

The MDR database houses MDRs submitted to the FDA by mandatory reporters including manufacturers, importers and device user facilities as well as voluntary reporters such as healthcare professionals, patients and consumers. For the purpose of this analysis, the MDR database was searched by a date report entered, brand name, product codes and presubmission number. Using the search criteria, we identified 324 MDR's pertinent to the dystonia indication.

For comparative purposes, the total number of MDRs for each PAC data set is presented in this table. The dates included in each PAC reporting period are presented below the table. Please note, that the 2014 PAC included more than one year of data. Also, note that the PAC reporting periods do not coincide with calendar years. The total number of MDRs included in the 2017 PAC data set is roughly the same as last

year's data set. There were 198 MDRs associated with adult patients and 68 MDRs in which the patient age was not reported and could not be determined.

In all PAC data sets, the majority of the MDRs were associated with adult patients. Within the 2017 PAC data there were 169 malfunction reports, 154 injury reports and 1 death report. A single report was associated with an adult patient and no pediatric deaths were reported. In the 2017 PAC data set, there were a total of 58 pediatric MDRs associated with patients ranging in age from 5 to 21 years old. The percentage of pediatric reports within the 2016 and 2017 PAC data sets was very similar. The average pediatric age was 14.4 years compared to an average pediatric patient age of 15.7 years in the 2016 PAC data set.

Although the majority of pediatric MDRs reported on label use of the device, it should be noted that off-label use of the device in patients under the age of 7 was reported in a

year old patient and a 6 year old patient in the 2017 PAC data. The 5 year old patient experienced skin erosion at the neurostimulator pocket which required device explant. Additionally, the 6 six year old patient experienced an infection that resulted in device explant. Both on-label and off-label MDRs were included in this analysis.

The majority of MDRs originated from inside the U.S. This is consistent with the reporting pattern seen in 2014, 2015 and 2016 PAC data sets. A more in depth review was conducted on the 58 MDRs associated with pediatric patients. The pediatric reports were individually reviewed to identify events which were clinically significant or concerning as defined by CDRH clinicians and reviewers. This table shows these clinically concerning adverse events and how frequently they were reported. I will discuss each of these events in detail in a moment. It is important to note that a single MDR may be associated with more than one patient problem,

therefore, more than one contributing factor may have been associated with each of the events presented in the table. Additionally, a unique event may be associated with multiple MDRs since patients are often bilaterally implanted or reports can be received from multiple sources such as a voluntary reporter as well as a manufacturer.

All twelve MDRs reporting device replacement, also reported device explant. In the twelve MDRs that reported both device explant and replacement, the most frequently reported patient problems were battery charging issues and lead fracture. Time to replacement couldn't be calculated in seven of the twelve MDRs and ranged from the day of implant to 5.1 years after implant with an average time to replacement of about 17 months. There were twelve MDRs that reported device explant without device replacement. Devices were explanted due to infection, battery charging issues, skin erosion, decubitus ulcer and lack of therapeutic benefit.

Worsening or return of dystonia symptoms

was associated with several different device problems. The reported problems that contributed to worsening or return of symptoms are provided on this slide. The most frequently reported contributors were battery charging issues and impedance issues. These issues resulted in device explant and unknown or unresolved patient outcome.

There were 14 pediatric MDRs related to battery and/or charging issues. These reports were associated with a variety of contributing factors which are presented on this slide. These battery charging related issues resulted in device replacement, no known impact on patient and loss of therapy. Patient outcome was unknown in seven MDR's.

There were 8 pediatric MDRs reporting infection. Limited information was provided on the potential causes of the infections reported in the MDRs. The only organism identified within the MDRs reporting infection was staphylococcus aureus. The remaining MDRs associated with infection, did not report a specific organism.

The location of the infections was reported in five of the eight MDRs and included three pocket site pulse generator infections and two lead site infections. The location of the infection was not reported in three MDRs. All of the infections resulted in full or partial device explant and two patients subsequently had their device replaced.

There were eight pediatric MDRs associated with electromagnetic interference or EMI. The reported sources of EMI included exposure to a computer tablet on a wheelchair using software with a digital imaging system that puts out ultrasonic waves as part of a class, security gates at a school library, security gate at an unknown location, working with magnets at school and unknown sources. The impact of EMI on the device is unclear based on the limited information provided in the MDRs. The information in the MDR suggests that EMI may be inadvertently changing device settings or turning off the device.

Potential growth related issues were

reported in five MDRs and the reported issues are presented on this slide. The ages of the patients associated with these reports range from 9 to 12 years old. Time to event from device implant date was able to be calculated in three of the MDRs and ranged from 2.2 years to 5.2 years. There were five MDRs associated with lead break or fractures. Three of these MDRs resulted in device replacement and in two MDRs it is unknown if or how the issue was resolved. The types of lead break fracture are presented on this slide.

In summary, a total of 58 MDRs were associated with use of the Activa Neurostimulator in pediatric patients. Infection and return or worsening or dystonia symptoms with the most frequently reported pediatric patient problems, the labeling does address the issue of symptom return or worsening and these events are known to occur with use of other neurostimulators. Other reported patient problems included infection and patient growth related issues are noted in either the device labeling or clinical summary.

The most frequently reported device problems were battery charging issues and impedance issues. Very limited information on the battery charging issues was provided within the MDR's. The device labeling states that issues with open circuits, such as high impedance, can occur without warning and impedance issues are also known to occur in other neurostimulators. Other problems such as charging issues, lead fractures or EMI that occurred within the MDR's are either noted in the device labeling or known device issues with neurostimulator devices in general.

As opposed to the 2016 PAC dataset, no MDRs associated with pediatric stroke or cognitive changes were reported within the 2017 PAC data set. No new patient or device problems were identified in the 2017 PAC data when it was compared to previous years.

I will now present information on the systematic literature review completed by the Division of Epidemiology. A literature review was

performed to evaluate adverse events following use of Activa for primary dystonia in pediatric patients. A string of search terms, identical to what was used in the previous literature reviews, was used search Pubmed and EMbase databases for the 12 month period. Articles were only included if they were reported on outcomes specific to primary dystonia and within pediatric populations. The search yielded 15 articles, 14 of which were excluded for the various reasons listed on this slide. There was only one article that met our criteria.

A retrospective chart review involving a case series by Krause et al examined a long-term safety of palatal DBS in eight pediatric patients. The main reason for surgical intervention or revision after successful implantation was the replacement of the IPG after battery expiration necessitating ten replacements in four patients. One patient needed revision of the IPG due to dislocation 11 years after the initial electrode implantation. One patient underwent bilateral

electrode revision three years after the initial palatal DBS.

Stimulation induced dysarthria limited further increase of stimulation amplitude in two patients and bradykinesia was induced by DBS in one severely affected patient with high stimulation amplitudes. Finally, one patient underwent several orthopedic surgeries due to severe contractors and musculoskeletal deformities resulting from long disease duration before DBS surgery.

In summary, no novel safety event was detected in the literature published since the last PAC. These findings are consistent with the conclusions from the systematic review conducted for the previous PAC meetings.

In summary, the FDA recommends continued surveillance and will report back to the PAC in 2018. Does the Committee agree with the FDA's conclusions and recommendations?

DR. HUDAK: Thank you. This is now open for discussion. Questions, this is the fourth

time but the first time for you, Dr. Zuppa, so please go ahead.

DR. ZUPPA: Just a quick question. Do you if those infections were at the skin site or if they were like full or meningitis and if they went into the central nervous system.

MR. MILLER: I don't think there was any information related to that in the MDRs but the location was listed. I can repeat that is you'd like.

DR. ZUPPA: So skin site?

MR. MILLER: So at the skin site? I'm sorry.

DR. ZUPPA: I'm just wondering because if it is a path that leads from the skin into the central nervous system, whether or not those infections extended into the central nervous system.

MR. MILLER: That information was not provided in the MDRs.

DR. ZUPPA: Okay.

DR. HUDAK: Dr. Cnaan.

DR. CNAAN: Avital Cnaan. I have question of the data from year to year. Could you identify if the same patient had a battery malfunction, whatever, in two different years or there is no way for them to find that?

MR. MILLER: I don't think there would be a way for them to definitively determine that in the MDRs data.

DR. CNAAN: Okay.

DR. HUDAK: Dr. Wade.

DR. WADE: Kelly Wade. Can you tell us if there was a difference year to year among the number of such things such as lead fracture or the electromagnetic interference? It seems like there are a couple of these MDRs that are in areas that over time may become less or over time could become more. So in these individual components is there a change over time?

MR. MILLER: We did not notice an increase or decrease really in any of the trends for the different adverse events but I could go back and try and look at the data to compare if

that is necessary.

DR. HUDAK: Dr. Sayej.

DR. SAYEJ: Perhaps one of my concerns here is looking at the data that is presented and looking at the number of malfunctions and number of injuries from 2014, 2015,

and 2016, year over year there has been an increase in the number of events reported. Overall, over the past four years there is definitely in the percentage of cases there is definitely an increase in these events as well. I understand that the injury issue is probably due to the physicians or part of the medical care but the malfunction events, is the company doing anything to address those issues. For example, the battery issue or the leak from the leads or any of these malfunction issues. What is the company doing about those things.

DR. MILLIN: So this is Courtney Millin, I'm going to take that question. So first of all, we can comment on what we're doing at FDA and we have some knowledge of what the company is doing

but we can't really speak to what they are doing as much. Just to sort of put this in context, we can't really compare the incidents or the percentages by year because there could be under reporting, there could be overreporting. So there are a lot of limitations in comparing those numbers. But we had a similar concern noticing that there is like a greater number and we feel that that could be because there is just a greater number of patients that are being implanted over time. So that was our take on it. We don't see any differences in the types of events that are occurring and this is a humanitarian use device. So I think from our perspective it is very similar to what we saw last year and the previous year. I don't know if that helps. Do you have any other questions on that?

DR. HUDAK: Dr. Anne. Oh sorry, go ahead.

DR. SAYEJ: Still just based on the number provided and the number of MDRs reported and the number of events, 14 to 20 percent of

malfunction rates seems pretty high to me. I'm not sure what is acceptable based on FDA policies but that seems to be quite high.

DR. MILLIN: Well, we try to weigh the risks and the benefits and we don't regulate the practice of medicine and so it is nice to have something that people can use if other things have failed. This isn't like a frontline thing that people would try in these patients. I don't know if you have anything else to add.

MR. MARJENIN: I mean when you're thinking about the types of free clinical testing that is done, so you're going to have non-clinical testing that is done to demonstrate a reasonable assurance of safety from say an electromagnetic interference perspective or other typical bench testing perspectives. And year to year there may not really be any actual updates to the device itself so just because we're coming here before the Committee year to year, there may not be any changes to the device year to year.

So in some cases, the devices that we

could be talking about here, they could have been implanted several years ago and we're just seeing events now. They may be from slightly older versions of the device or they just may be the version that was approved. So I think and just to echo what Courtney was saying, it is kind of hard to put -- I mean thinking about it in the context, you are talking about a relatively small number of patients out there anyways and a relatively small number of events and it is still subject to all the limitations of the MDR reporting system.

So I think the important thing just to echo what has been said already is that year to year while you may see a slight variation in the number we certainly haven't been seeing any spikes in the numbers of events that have been reported and we haven't been seeing any new types of events that have been reported so that's why we feel pretty confident in our recommendations.

DR. PEIRIS: I'd like to perhaps address the question unless -- I want to acknowledge and appreciate the point that you're making that these

trends sometimes can certainly seem like there is a greater issue developing. I think as we pointed out already there are deficiencies with respect to the MDR reporting system which we've continued to be very clear and transparent about. We also understand that some of these devices, the duration of implant may be increasing as well so you want to incorporate that into your considerations of numbers increasing. I think you already very clearly stated the overall numbers of implants and adverse events are relatively small. We also have to clarify the severity of the type of event that is occurring. So a number of issues are a little difficult to be a little more poignant about on when trying to assess whether this is a significant factor increase or not.

DR. CNAAN: Avital Cnaan. I kind of want to echo the concern. The limitations of the system are what they are and clearly we don't know if these reports are from devices that, by this point, are older that may explain the increase. I recognize that. With that said, I think asking

maybe the sponsor if they are doing anything to consider some improvements in the device that there is a lower number at least in the newer ones of these device malfunctions. Maybe the FDA should consider that at least. If it is all the older devices, fine. I think that the sponsor might know if these are the older devices.

DR. HUDAK: I think I recall in a past meeting that there was some focus by the manufacturer on some of these issues related to device function and they had made some improvements and I think time will tell whether or not, for instance, battery issues and so forth. There will be some perceptible decline in the number of incidences or extended lifetime of the battery. That remains to be seen, I guess.

Any other questions? If not, we will do the electronic voting on the recommendations on the screen in front of you. Okay everybody apparently has voted. So we'll start, Dr. Kishnani, with you.

DR. KISHNANI: I concur.

DR. HUDAK: And we'll go around the table starting with Dr. Cnaan.

DR. CNAAN: I concur with the hesitations that I expressed.

DR. ZUPPA: Dr. Zuppa, I concur.

DR. CALLAHAN: David Callahan, I concur.

DR. WHITE: Michael White, I agree.

MS. MOORE: Erin Moore, agree.

DR. CATALETTO: Mary Cataletto, I concur.

DR. WADE: Kelly Wade, I concur.

DR. ANNE: Premchand Anne, I concur.

DR. KASKEL: Rick Kaskel, I concur.

DR. SAYEJ: Wael Sayej, I concur with the reservations I mentioned earlier. I think that there are 581 devices implanted in children over the period of time and there were 122 reported injuries and 82 reported malfunctions. That equates to about 35 percent of the cases based on this data. To me, that is a high number and I hope that the FDA will address this with the manufacturer and see if they're doing anything

about it to correct this.

DR. TURER: Christy Turer, I concur.

DR. HUDAK: Okay, so thank you, Mr. Miller. We are, again, unanimously in favor of continuing your surveillance on this product.

We have two more to do. I think we'll try to power through unless there are objections. Are the people who will do the Impella presentation present. Yes, okay so if you can come to the table and the podium. And as Dr. Aggrey is making his way up to the podium if staff sitting at the table could introduce yourselves.

DR. LASCHINGER: John Laschinger, Medical Officer in the structural heart device branch of the Division of Cardiovascular Devices FDA.

MS. BAUER: Kelly Bauer, I'm a nurse consultant in the Office of Surveillance and Biometrics, Division of Post Market Surveillance.

DR. HUDAK: Thank you. So Dr. Aggrey, the floor is yours.

DR. AGGREY: Good morning. My name is

George Aggrey. I'm an epidemiologist at the Office of Surveillance and Biometrics, CDRH. I will present CDRH annual review for the Impella RP HDE including a review of the medical device reports and the published literature since our last briefing in 2016.

The Impella RP system is a minimally invasive miniature percutaneous circulatory support system for the right ventricle. The main component is a 22 French micro (inaudible) pump catheter. The Impella RP system is indicated for providing circulatory assistance for up to 14 days in pediatric or adult patients with body surface area or BSA equal or greater than 1.5 m2 who develop acute right heart failure or decompensation following left ventricle (inaudible) or LVAD implantation by cardiac infarction, heart transplant or open heart surgery.

A total of 339 Impella RP devices were

sold in the U.S. in 2016. 288 devices were implanted including 8 implants in pediatric patients less than 22 years old. The sponsor is required to conduct (inaudible) studies to monitor the

(inaudible) and probable benefits of the Impella RP device. The Impella RP prospective study, or PS1, is a

single arm with multicenter study enrolling 30 patients from sites who are at the age of 18 years and have a BSA equal

or greater than 1.5 m2. Patients will be followed for up to 180 days post device explant. The primary end point is survival at 30 days post device explant or hospital discharge whichever is longer or to induction of anesthesia for next therapy.

patients are currently enrolled in this study. Their ages range from 21 to 81 years and the mean age is 60 years. Patients enrolled in the prospective study include one patient, age 21,

who is within the CDRH pediatric age range. A total of 18 patients met the primary end point surviving to 30 days post successful (inaudible) or hospital discharge or to induction of anesthesia for next therapy.

Of the 18 patients that met the primary end point, remained alive at 180 days post device explant. Three

patients died between day 1 and 180, one patient is alive past days but not yet 180 day time point and one patient

transitioned to next therapy. Eight patients died prior to meeting the primary end point. The patient who transitioned to next therapy also died in hospital. Thus, 9 patients died in hospital or prior to 30 days. In total, 12 patients have died in this study.

The primary end point of 69.2 percent, 18 out of 26 is comparable to the survival rate of them in their recovery rate ID study which was 73 percent. Although not a focus of this study, (inaudible) pediatric patient was treated in PS1

for right ventricular failure (inaudible) following an LVAD inserted for left ventricular failure due to nonischemic cardiomyopathy. The patient was transitioned to Centrimag device for additional IV support and was discharged following a successful wean.

The adverse events reported in the perspective study were major bleeding events reported in 42 percent of patients,

out of 26 and hemolysis reported in 35 percent of patients, out of 26. There were no events of pulmonary embolism. All

adverse events including death had been (inaudible) reviewed by the clinical event committee, CEC. There were no device or procedure related adverse events in the pediatric patients. One major bleeding and two hemolytic events were (inaudible) as definitely related to the device and procedure. One death was (inaudible) as probably device and procedure related.

This slide presents a summary of the death events that was (inaudible) as probably

related to device and procedure. The patient was a 72 year old female who was admitted with severe left and right ventricular failure and ejection fraction of 10 percent. The patient had an LVAD Impella RP implanted at the same time. The Impella RP was explanted on the sixth day of placement. After explant, the patient developed multiorgan failure, multisystem organ failure, and died. The immediate cause of death was reported as sepsis due to cardiogenic shock.

The Impella RP pediatric study, or, PS II is a retrospective single R multicenter study designed to ensure that all Impella RP use (inaudible) pediatric heart

(inaudible) are cultured. Since overall enrollment was anticipated to be low in pediatric hospital sites, all pediatric patients implanted over five years would be enrolled until a target number of patients is achieved. The indication for Impella RP use in

pediatric patients age 15 to 17 years of age would be as equal or greater than 1.5 m2 are the same as for PS I. (Inaudible) duration and the primary end point are also the same as for PS I study. Soon the last part meeting one site approved for general HDE use has enrolled one patient. Two pediatric sites are being trained to use the Impella RP.

The patient who is currently enrolled in the pediatric study is a 16 year old male diagnosed with a right ventricular dysplasia who experienced cardiac arrest at home.

(Inaudible) and initiation of inotropes significant biventricular failure led for the need for mechanical supplementary support with a left sided assist device, Impella CP and a right sided Impella RP device. Hemodynamic

stabilization was achieved and both devices were successfully weaned at day 7. The patient was discharged home neurologically intact.

FDA is working with the sponsor to specifically increase enrollment at designated high volume pediatric centers. The sponsor plans to increase enrollment in the pediatric PS II by targeting enrollment of high volume pediatric cardiac centers as HUD sites. (Inaudible) have been identified by the sponsor. These targeted recruitment efforts were (inaudible) over the next few months. With these efforts, the sponsor is hoping to increase PS II enrollment to five to six patients in 2017 and four to five patients per year in year four and five.

The Impella RP was also implanted in six patients who are within FDA pediatric age range. The size currently outside either of the post approval studies. There reason for Impella implantation was right ventricular failure following LVAD implantation in one patient, post

cardiogenic shock in two patients, pulmonary hypertension in one patient and heart transplant in one patient. The reason for implantation for right ventricular failure was unknown in one patient. Of the six patients, three patients were successfully weaned and two patients, one with post cardiogenic shock and the patient with pulmonary embolism were unable to be weaned from support and died. The outcome in one patient is unknown. Per the sponsor, other clinical information on these patients were not available at the time of this data extraction.

As such, the literature was conducted for studies on the Impella RP. Two articles were identified. One was a case report on the use of Impella RP and the other was a publication on the recovery right IDE study that was submitted to FDA for the HDE approval which has already been presented to the PAC.

This slide presents a case report. (Inaudible) are included in the executive summary. The patient was a 70 year old female with a

history of non-ischemic dilated cardiomyopathy and ejection fraction of 10 to 15 percent. The patient was implanted with a HeartWare ventricular assistive device and successfully supported with an Impella RP device. There were no device related complications.

(Inaudible) present a medical device report review. The FDA searched the MDR database for all reports associated with the Impella RP from November 1, 2015 through November 30, 2016. The query resulted in the indication of six MDRs. There were no MDRs involved in pediatric patients. There were five male patients and one female ranging in age from 44 to 68 years with a mean age of 59 years. Five MDRs were reported in the U.S. and there was one MDR reported from outside the U.S. in Denmark. There was one death and

five injuries.

This table shows that reported problems in the MDRs by the type of event in this year's analysis compared to the 2016 analysis. There were two MDRs related to thrombosis or clot formation in the device which we also identified in last year's analysis. And that event involved a 56 year old male in which the biomaterial wrapped around the Impella, likely interfered with (inaudible) causing alarm and pump stops. According to the instructions for use, the pump should have been exchanged after the pump stopped. Eventually, the decision was made to change the pump and to change to ECMO. However, the patient expired prior to ECMO placement.

The manufacturer concluded that the patient and the line condition of PFO and blood shunting also contributed to clot formation. There were two MDR's where they revised the (inaudible) pump remover. The firm’s investigation determined that a device detachment was caused by a

high cumulated load imparted on the inflow cannula during use. The load was likely secondary to challenging device placement and/or improper positioning during use. Corrective actions have been implemented by the firm who later enhanced clinical treatment to device uses.

The firm has also explored additional preventative actions related to the use of fistulas to improve the cannula bonding process and will update the FDA (inaudible) requirements. There was one bleeding event where a CT scan reviewed a large (inaudible) bleed of unknown origin requiring the administration of blood products and surgical evacuation of the hematoma. There was one MDR where there was difficulty in positioning the pump in the position resulting in alarms and increase plasma free hemoglobulin levels. The pump was exchanged and the hemolysis resolved. The family later withdrew support due

to the patient's medical condition. According to the IFU, performance level may vary due to suction or incorrect positioning. The instruction for use addresses troubleshooting tips to mitigate these issues. All of the events reported in the MDR are described in full detail in the executive summary.

To summarize key points of the MDR review. There were no pediatric patients reported in the MDRs. The risk of thrombosis, hemolysis, bleeding and position issues reported in the MDRs have been reported in the IDE, are addressed in the IFU and reflect known complications of this type of device. Corrective actions have been implemented by the firm related to device attachment. Additional actions are ongoing and the FEM will update the FDA panel reporting requirements. Through additional discussions with the firm, it was identified that one MDR was related to an adult PAS patient. There are

no other safety concerns at this time.

FDA will continue surveillance and report updates of the following PAC in 2018. There are no distribution number, the mandated post-approval study review, a literature review and the MDR review. FDA would like to ask the Committee, I agree with the FDA's conclusion and propose approach. Thank you.

DR. HUDAK: Thank you, Dr. Aggrey. This is open for discussion. Dr. Kaskel.

DR. KASKEL: Just a question. Why are they having so much trouble recruiting patients again?

DR. AGGREY: The problem is with the recruitment in the pediatric patients, PS II. PS I is almost complete. The study was designed to enroll patients ages 15 to 17 years with body surface areas of 1.5 m2. Enrollment has been concentrated on all issue (inaudible) but this one has been encouraged to concentrate on looking at specialized pediatric centers where they are

likely to be high volume patients to be treated with the device.

DR. LASCHINGER: The adult study is 85 percent enrolled, so there is not a problem with enrolling in there and that captured one pediatric aged patient that was treated at one of the adult sites. The PAS II is specifically designed to capture all pediatric use wherever it occurs in the United States because we recognize that a lot of these children would be not treated at adult hospitals where the PAS II is concentrated.

The problem is in that the roll out that the company has several other devices that are adult sized devices and they are used to dealing with those centers and they didn't concentrate on pediatric centers specifically for this device and there has only been a couple of pediatric centers that have actually asked for it. We're making sure, along with the company, that they go out and actually talk to high volume pediatric centers such as would be Washington Children's Hospital or Texas Heart Hospital at Texas Children's Hospital,

excuse me, Boston Children's and places like that so that the device, if the hospital wants it is available at these sites. In the end, it comes down to whether or not the physicians want to use the device at the center where it is at but that's the crux of the matter.

DR. HUDAK: Dr. Zuppa.

DR. ZUPPA: But if you look at the indications for it, a lot of them are adult indications. A kid is not going to have an MI. We use LVAD sometimes but not all the time so I think the indications are more adult problems than they are pediatric problems.

DR. AGGREY: I think there are two possible indications. One is patients who need a device after LVAD implantation in the congenital anomaly. Another patient may also have MI, open heart surgery as well. So we believe that patients who may need LVAD after implantation who develop right ventricular failure after LVAD implantation will fit in the pediatric category.

DR. LASCHINGER: Even in the pediatric

centers, obviously, there is the size constraints of the device. The child needs to be 1.5 m2 body surface area which means usually adolescent or above. So we're certainly not going to capture anyone below that age range either.

DR. ZUPPA: And then if you look at, in general, heart disease surgery that is usually happening early on in life.

DR. PEIRIS: I just want to resonate with the question that was asked initially about why, and obviously this entire discussion is about why we haven't had more effective and robust pediatric enrollment. The purpose of this process was to actually gain pediatric enrollment and monitor that. We are very cognizant of this issue, we've brought it to the attention of Abiomed.

Abiomed has developed a plan that they feel will be consistent with achieving the enrollment parameters that were designed for the PAS II. We have suggested other centers that are high volume in pediatric cardiology that could potentially be centers to gain more enrollment and

we also agree that novel devices should be utilized most safely in centers that have a great expertise and staff teams infrastructure process to ensure that there are few adverse events in managing those patients with novel devices. So I just want to acknowledge and recognize the points that have been brought up today.

DR. HUDAK: Okay I think we're ready to do the electronic voting on the recommendations on the screen in front of you. Dr. Kishnani will start with the verbal roll call.

DR. KISHNANI: I concur.

DR. HUDAK: And then around the table I think we'll start with Dr. Turer.

DR. TURER: Christy Turer, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. KASKEL: Rick Kaskel, I concur.

DR. ANNE: Premchand Anne, I concur.

DR. WADE: Kelly Wade, I concur.

DR. CATALETTO: Mary Cataletto, I concur.

MS. MOORE: Erin Moore, I concur.

DR. WHITE: Michael White, agree.

DR. CALLAHAN: David Callahan, I concur.

DR. ZUPPA: Athena Zuppa, I concur.

DR. CNAAN: Avital Cnaan, I concur.

DR. HUDAK: Okay another unanimous vote in favor of continuing monitoring. We can move on if folk are here to the last presentation of the day, yes. All are here. So I have introductions from staff at the table first. Could you introduce yourselves to the Committee.

MS. RICKETTS: Cathy Ricketts, I'm in the Office of Surveillance and Biometrics. I'm a nurse analyst.

DR. SILVERSTEIN: I'm doctor Silverstein, I'm a medical officer in the Division of Reproductive Gastro Renal and Urological Devices and the Renal Devices Branch. Good morning and thank you for moving things along.

So we presented this a couple of times before so I'm going to run through some of the introductory slides. This information is also provided in your executive summary. The

indications for use for the pediatric HDE we'll be talking about the Liposorber LA-15 Systems indicated for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis. When either standard treatment options including corticosteroid and/or calcineurin inhibitors, treatments are unsuccessful or not well tolerated and the patient has a GFR measure of renal function greater than 60 ml per minute or the patient is post renal transplantation and has reoccurrence of FSGS.

Just a brief background, again, there is a lot in your executive summary. FSGS is a kidney disease resulting in severe proteinuria and usual nephrotic syndrome. The majority of patients reach end stage renal disease which means they require dialysis or kidney transplantation within ten years of the initial diagnosis. Previous reports showed that probable benefit in safety for adults and children with FSGS treated with the Liposorber LA-15 System, the HDE

therapy for FSGS was approved in 2013 and this is an annual update of the PAS.

Briefly, this is a device description. So the patient would be here on the far left. It is an extracorporeal therapy so blood is removed from the patient and then run through a circuit similar to what we see with hemodialysis. So blood is removed from the patient generally by a catheter. It then goes through a blood pump because the blood needs to get through the system and it is not going to generate that on its own. It then runs through a plasma separator so plasma is taken one place, the red blood cells, white blood cells are taken to another place. The red blood cells and white blood cells are stored here. The plasma then is taken out and run through the Liposorber columns called the LDL absorption columns, they absorb LDL cholesterol. Once that is then finished, it runs back and is reconnected with the blood cells and then returned back to the patient and this goes on for several hours.

So the purpose of this is to isolate the

plasma, restore the blood cells and the restore the blood back to the patient that is cleansed of LDL cholesterol and other potential substances which might be removed by the columns. And that is an important point. It is used for patients with familial hypocholesterolemia where LDL cholesterol is removed. But in these patients, we believe that the benefit goes beyond that of just removing the LDL cholesterol.

So after the approval of the HDE, we designed a post-market study with the sponsor and the objectives were to assess the safety, specifically adverse events during and one month after the final Liposorber treatment and the probable benefit, which in here, is measured as classically as measured in studies with renal disease. The achievement of complete or partial remission of nephrotic syndrome, one month after the final Liposorber treatment. And I want to emphasize that the remission of nephrotic syndrome is an extremely important sign that a disease may be abating and we also would be assessing GFR.

The criteria for the study with patients age under years of age, body weight greater than 18 kg at baseline.

This originally was 21 but in discussions with the sponsor we decided that it was safe to lower that down to 18. It included patients with FSGS and again with persistent nephrotic syndrome who were resistant to or intolerant to therapy and had reasonably good renal function preserved.

The treatment schedule is the patients come in over a 9 week period of time and receive 12 treatments according to a certain schedule. And the study included 32 patients and so far as I'll go into, 8 patients have been treated.

So the interim results so far looking at the probable benefit, shows that so far 8 patients have been treated with the device. Now because the follow up period is a long period of time, not every patient has a full follow up period that has already been assessed. So far, six patients have had three to six months of follow up data

after the last Liposorber treatment, so it is after several months of the Liposorber treatments.

If you look at remission of nephrotic syndrome, again, criteria that would assess the resolution or improvement of renal function. One month after the final treatment, no patients had a complete remission, two had a partial remission, three had no remission whatsoever and one it was unclear at the particular time, probably a data collection issue. Three months after the final treatment, one had a complete remission, two partial and three had none and these patients followed along their line. So the two that had partial continued to be that way. And then finally, after six months, one had a complete remission, two partial and three had no remission. Down at the bottom there are some definitions. This is in your executive summary. How do we define complete or partial remission. It depends upon the degree of proteinuria.

We also look for probable benefit at glomerular filtration rate shown here on the top.

Urine protein and creatinine, LDL cholesterol and we also, as an exploratory measure, we looked at SuPAR with is a circulating factor that has been identified in some patients with FSGS but certainly not all of them. So I'll run through this. Here we have the six patients here on the left hand column. The baseline GFR is shown here and you can see if you just look at the column next to it that the 3 of 6 month EGFR is very, very stable. In the vast majority of the patients and went up a little bit in a couple of them and went down a little bit in a couple of them. Just to make note of patient five, the GFR range is 0 to about 120. So this result of 170 probably reflects a very, very abnormally low serum creatinine which is used to assess GFR and it probably isn't a real number. So going from 170 to 130 does not mean that there is decline, it is probably a lab phenomenon.

Very important measure is the urine protein and creatinine. Again, proteinuria is a very important sign of improvement of kidney

function. And you can see as shown in the red font that three patients had a significant drop in their urine protein to creatinine ration. Patients two and six really had no change and the only patient who we saw an increase was patient four.

LDL cholesterol, I'm not really going to belabor on this too much. The point of this therapy for patients with FSGS nephrotic syndrome is not really to remove LDL cholesterol. Now certainly patients with nephrotic syndrome can have hypercholesterolemia and this could be a benefit. But in a short term, we don't really consider this to be an end point that I think is meaningful. But basically, you can see the numbers were kind of all over the map.

And finally, we did discuss with the sponsor about measuring SuPAR because we thought it might give an indication about which patients might be benefiting from the therapy. So the theory is that if it is circulating factor, SuPAR and there are probably several others in

patients with FSGS. If you can remove the circulating factor could that be correlative with the improvement of patient symptoms. We really didn't find that. These numbers, again, were kind of all over the map and we really didn't see any relationship whatsoever between SuPAR and the improvement of symptoms. Again, I want to state that the majority of patients probably do not have SuPAR as their circulating factor. Some do, some don't, but the majority probably don't. We don't know exactly what these numbers mean in these patients. It was an exploratory end point for that purpose only.

I want to just briefly talk about safety. Going back a little bit, when we initially approved the HDE, we didn't have a lot of safety data on patients with FSGS treated with the device. So what we did, was we felt it was reasonable to extrapolate safety data from patients or I should say children with FH treated with the device. We felt that if anything, children with FH, familial hypercholesterolemia

probably have as high if not a higher risk profile then patients with FSGS so we felt that it was reasonable to look at the data obtained from children with FH treated with the device. And you can basically see on this slide that most of the events that had been thought to maybe occur with the Liposorber were not reported to occur in any children. Again, this is over 1000 treatments with the device. There were a few adverse events like infection, nausea and vomiting, hypotension which occurred pretty rarely in children. So this gave us confidence that this data could be extrapolated to children with FSGS and that these side events were relatively infrequent.

So the interim results for the safety since the last PAC meeting for this device and for patients with FSGS, we saw two adverse events that were reportable. Both of these occurred while the patients were receiving therapy with the device, so not after that period where the data is also being collected. In one patient, the patient developed fever, diarrhea and abdominal pain

considered to be of moderate severity. It did require a brief hospitalization. The patient recovered and it was believed not related to the device itself. The second patient developed fever and a possible infection. It proved out to be a viral illness. Again, moderate severity, did not require a hospitalization and believed not related to the device itself.

It is important to remember that there are three factors that can cause adverse events in patients getting therapy. Number one, is they have FSGS and nephrotic syndrome which itself can cause symptoms. Number two, they are being treated with the device. And the third factor is these patients have catheters which can cause infections and other problems. So multitude of reasons why patients can have symptomotology.

The systematic literature update review, basically we did a search strategy including looking for the words Liposorber, LDL and apheresis. Looking for all comers, all patients. We found 109 articles but many of them had to be

excluded because they didn't involve a clinical study, there was no use of the Liposorber LA-15 System mentioned, it might have been another similar but not that exact device. Nineteen didn't include any pediatric patients and one involved and indication other than FSGS. So basically, we weren't able to find anything new regarding the probable benefit of safety for pediatric patients treated with the LA-15 System for FSGS.

Our MDR report review included the search using two product codes. Product codes are basically categories. Their codes apply to categories of devices that the FDA uses just to categorize information. The two product codes we use were MMY and PBN and you can see that they apply to certain types of devices. The period dates that we included in this search were January 1 through December 31, 2016. We found six MDRs doing the search through the product code on our system. One was a pediatric patient and five were adults. For the pediatric patient, it was a 14

year old male who had recurrent nephrotic syndrome associated FSGS after kidney transplantation. The patient developed a Grade III anemia after the 17th treatment. And it is important to note that the labeling does address the possibility of anemia with LDL apheresis procedures. And the manufacturer narrative of this report sites this could be secondary to cumulative blood loss by residual blood in the extracorporeal circuit, well known to happen in patients who get extracorporeal therapy and it could have also been to repetitive blood sampling which is necessary for these patients.

There were five reports in adults, two resulted in death. One patient developed death from cardiac arrest and the other one from a myocardial infarct. There was no clearly stated device causality in either report. The manufacturer noted in the report of the MI that the LDL-A treatment may have been relevant to the patient's sudden change. The two reports specifically, there was a 72 year old male who

expired one day after the eighth LDL-A treatment from sudden cardiac arrest. A 50 year old female expired after receiving her sixth treatment of the third course of LDL-A treatment. This patient suffered myocardial infarct. Again, these are adults with familial hypercholesterolemia who were getting chronic therapy with the device. So again, familial hypercholesterolemia, these patients are well known to develop cardiovascular disease, especially later on in life.

There were three adult reports of serious injury regarding an 82 year old male, an 82 year old female and an unidentified patient. All of these events involved a patient experiencing severe hypotension with either a loss of consciousness or shock. In each case, the LDL-A therapy was discontinued and the patient recovered and there was really no clearly stated causality.

In the 82 year old male, the patient developed hypotension after the first LDL-A treatment and loss of consciousness. It wasn't

clear exactly why this happened. Hypotension, again, is in the labeling and instructions for use as a known adverse effect, probably related to either cardiovascular disease underlying condition in the patient or the fact that the patient is getting treatment on a extracorporeal circuit. The 82 year old male developed hypotension and shock minutes after the treatment. The problem in this patient was is the patient also received hemodialysis on the same day. So basically, the patient was exposed to two therapies requiring extracorporeal therapy on the same day. It is not exactly clear what the time period was between the therapies. I'm sure that they felt it was medically indicated but that was probably the reason. It may have just been an intolerance to the combination procedure. The last unidentified patient was hypotension and shock, 15 minutes after an LDL-A treatment. It was known after the fact that the patient received an ACE inhibitor, angiotensin-converting enzyme inhibitor, on the same day and it is

contraindicated to get therapy with the LDL-A, apheresis device, Liposorber device while also receiving angiotensin-converting enzyme inhibitor because of a bradykinin response that has been known to occur.

Our conclusion from the MDR review were in 2016, there were a total of six MDRs involving significant adverse events. Two resulted in death, four resulted in serious injury. There was no mention of specific device related issues, however, the manufacturer investigations could not completely exclude the relevance of the treatment related to the outcomes. Again, several of these events including hypotension, are known to occur with the device. The known inherent risk with the use of the device such as anemia, shock, hypotension and dyspnea which were explained, are addressed in the instructions for use and also in the labeling for the device and it is also well known there is a contraindication of concomitant use of an ACE inhibitor while receiving therapy with the device.

So our considerations are that we believe at the FDA, that there are certain items that may benefit from modified labeling. There are some issues that we intend to discuss with the sponsor and ascertain if this might be a path to proceed with. We believe there might be increased potential of development of anemia after repetitive LDL-A treatments. Again, anemia is listed in the adverse events known for the device and it might be related to cumulative blood loss by residual blood in the circuit or related to repeated blood sampling as was noted in that one patient. So there may be some modified labeling that could potentially benefit patients.

We also believe that the combination treatment of hemodialysis in LDL-A therapy on the same day could increase the risk of hypovolemia. This certainly would not be something that would be related to something the sponsor has done it would just be related to, I think, just sort of practice of medicine. I would think this would be relatively straightforward unless a patient

absolutely requires hemodialysis on that day that you wouldn't give LDL-A therapy and hemodialysis on the same day. Its potential with this could be modified in the labeling but also this goes into, again, the practice of medicine.

So our recommendations are the CDRH believes that the device labeling could potentially be enhanced related to issues of the causes of anemia and the risk of hypovolemia with the device used on the same day a patient gets some other form of extracorporeal therapy and we intend to discuss these issues with the sponsor and we found those discussions in the past to be very, very cordial and productive. We will continue surveillance and report of the following to the Committee in 2018 including the outcome of the labeling review in discussions if there are any changes. We will also provide the usual distribution numbers, MDR review results and literature review results.

So the final slide, does the Committee agree with CDRH's conclusions and recommendation.

DR. HUDAK: All right so this is open for discussion. Dr. Zuppa.

DR. ZUPPA: Hi, thank you for that. I guess my first question, well the answer to my first question, the second question. Do some patients have central venous catheters just for the sake of this treatment?

DR. SILVERSTEIN: Yes these are patients who have a GFR of at least 60 mls per minute so basically they would definitely not qualify for hemodialysis. You have to have a GFR, typically of 10 mls a minute or lower or have other reasons to need hemodialysis emergently. So these patients would not be receiving hemodialysis unless there is some unforeseen reason why they would need a catheter. These patients are getting a catheter inserted specifically for the Liposorber therapy and when the Liposorber therapy ends in several months the catheter is removed. So it is going to require a tunneled catheter for sure.

DR. ZUPPA: So the only adverse event

that I saw that could be catheter related was bleeding at the site. Kids with nephrotic syndrome are prethrombotic and I'm just wondering if there were adverse events that were associated with a catheter that was in place for the treatment. Would those be attributed to the treatment because the catheter wouldn't be there otherwise and what the surveillance for clots were in this population.

DR. SILVERSTEIN: That is something we've debated because it really isn't the device. But it is something you need to get treated with a device. So you wouldn't use an AV fistula or a graft for whatever reason, maybe in a patient who already was on dialysis and got recurrence of the disease after kidney transplantation which is in the indications for use. We wouldn't use that anyhow, you would probably use a catheter. Fortunately, that issue hasn't really arisen yet but I would probably consider that to be device related because I don't think that you can get treated without having a catheter. It is

debatable. It is very possible that the catheter can get infected for reasons completely unrelated, that it could have been mishandled et cetera. So there wasn't proper technique for cleaning the catheter. That would be something that would certainly have to make us think twice but I would probably consider it device and/or procedure related, I would think so.

DR. ZUPPA: I'm worried about infection but I'm worried about clot, catheter associated thrombosis, specifically in this population.

DR. SILVERSTEIN: Well these patients are getting anticoagulation with their therapy. You couldn't do this because the blood is moving outside the body. You have to use anticoagulation and there are anticoagulation related adverse events listed in the labeling in the instructions for use. But that certainly is a concern in the same way that bleeding can be a concern. Remember, after the patient finishes a therapy they go home, the catheter is locked with heparin. And there is certainly the risk that if somebody

doesn't know there is heparin in that catheter hub, they can infuse heparin into the patient. We all know that's happened.

So these catheters should be clearly labeled on the outside of the hub that they're locked with heparin and there should be the right type of precautions. But you're raising a good point. Those are concerns that could always result from having a catheter. It comes down to what we believe is a benefit risk issue. I didn't really want to get to much into FSGS and nephrotic syndrome but these are patients who have reasonably good kidney function but they are not responding to therapy at this point.

In other words, they're starting to show a decline and as Dr. Kaskel and Dr. Portman know better than anybody, these patients are extremely difficult to treat and you're basically looking at a decline into dialysis or kidney transplantation. So we have to start to say to ourselves, if this therapy can delay that progression maybe cure, but delay that progression, then the question is

that's the benefit versus the risk of having a catheter. That is always the debate.

So good questions, and that's something that we hope that when people decide to put patients on this therapy with the device that they're making that choice with that in mind about what are the benefits and what are the risks for the patient and discussing those with the patient and the family.

DR. HUDAK: Dr. Anne.

DR. ANNE: I'd like to make two quick comments. The first comment is that in the setting of renal disease, the typical dyslipidemia that you expect to see is elevated triglycerides and also elevated LDL. Now the LDL could be at a lower level because of being triglyceride (inaudible) and they are small dense LDL particles. In this table that we are seeing here, 50 percent of the patients at baseline and 50 percent of the patients at three and six months have significant LDL elevations. So in the context of what I was trying to say, I guess is,

in the context of elevated triglycerides, the more appropriate thing to measure would be apolipoprotein B rather than monitoring the LDL levels. So that is point number one.

Number two is that in 2011, the American Academy of Pediatrics put out expert guidelines on dyslipidemia management and they actually promote earlier management of these, statin therapy or whatever appropriate therapy there is. So I don't think we can necessarily dismiss the LDL levels based on these levels here in this table or whatever else. I think these need to be taken a little bit more seriously and just monitored a little bit more accurately with the apolipoprotein B instead of the LDL itself.

DR. SILVERSTEIN: So you raised a lot of important points and many good points. So the first thing is, is if we look at the table except for one patient, the LDL cholesterol levels declined or were stable. So I do think there is some evidence that the device was maybe removing some of the LDL cholesterol. Now you raised, it

is a -- about the apolipoprotein B I think we can certainly discuss that with the sponsor and I'm going to be talking with them afterwards and we'll talk with the investigators. I think that is a reasonable --

DR. ANNE: It is an easy test.

DR. SILVERSTEIN: But the lipid profile gets a little bit complicated. Because lipid profile does change -- it does make a difference what your GFR is but it also makes a difference if you have nephrotic syndrome. So it is a complicated set of issues related to the lipid profile itself. Generally, what we do with patients with nephrotic syndrome, if they have an acute episode, we don't put them on lipid lowering agents because of the potential risk of statins. If patients have unremitting nephrotic syndrome, we might definitely consider putting them on a lipid lowering agent, depending upon what the profile may be. But it gets a little bit complicated because you have chronic kidney disease and you have nephrotic syndrome and the

types of lipid profiles for those two different categories aren't identical.

But you raise a very, very good point. And I didn't mean to minimize the importance of the LDL cholesterol here, I meant it more in relation to the fact that the mechanism of removal of LDL cholesterol is probably not the major factor helping these patients. We certainly don't know exactly what the device is removing, we believe there might be inflammatory factors, there could be circulating factors et cetera.

We know that inflammation contributes to the progression of chronic kidney disease, typical inflammatory mediators that we all know. So I apologize if it sounded as if I was sort of delegitimizing these -- I was sort of just trying to say it doesn't relate, necessarily, to the mechanism in which the device is helping these patients. But to your point, patients probably do have full lipid profiles available who are getting treated with this device and we can certainly ask for that information.

DR. ANNE: I think my emphasis is more on the chronicity of the disease process rather than the acute setting, per se.

DR. HUDAK: Dr. Kaskel and then Dr. Kishnani after you.

DR. KASKEL: Rick Kaskel. So this is the perplexing problem of the nephrotic trial failing to respond to everything walking around being at risk for infection, sepsis, cardiovascular events. Often there is no way to treat the edema effectively even when they become refractory to all the diuretic therapy. So this is at the end of the line and that's why this offers some hope. We're all waiting to see more evidence that we can sustain prolonged remission with this treatment.

Some of the molecules that everyone is hoping they're removing that are not yet identified are possibly small molecules that interact with the lipid complexes and effect the podocytes. That, I think, one of the targets here is what is happening at the podocytes by removing

these substances. I think there are some hurdles and I know at our place, the hurdles involve being able to say to a family, listen, here is the data, small numbers. Here are how many kids go into prolonged remission or improve the outcome. That is what is lacking because we don't have a substantial body of evidence yet. But for recruitment purposes, the sponsor needs to give as much forward to us to provide evidence that this is worth having a catheter inserted into a vein, a large vein for treatment and the time commitment for the study.

The second thing that we've experienced with this and this may be beyond the scope of this discussion, is inherent problems in an institution trying to prescribe this therapy and having the regulatory issues like the nurses who would do dialysis or plasmapheresis buy into it. That is the second thing that happened at our particular place and I'm not sure how you solve that from the sponsor's standpoint.

But I think the community, the pediatric

nephrology community is waiting for more positive results from the use of this technique.

DR. HUDAK: Dr. Kishnani has a comment on the phone.

DR. KISHNANI: Yes, hello. My question and comment are the following. In terms of the one case where hemodialysis had been done and there was actually a death from it, are there other reports, I know where a combination of hemodialysis and this device were used. Of course, it may not have resulted in death but where there were reports of other adverse events like drop in blood pressure, et cetera. That was number one.

Number two was based on the understanding that ACE inhibitors can be very problematic in this setting. Is this part of the current label or as we're in discussion, could this also be considered (inaudible).

DR. SILVERSTEIN: Just one clarification. The patient who received LDL-A therapy and hemodialysis in the same day did not

die. The patient developed hypotension but the death was in two other patients.

DR. KISHNANI: Thank you for that.

DR. SILVERSTEIN: But your point is well taken, though, about that risk.

DR. KISHNANI: And in terms of the ACE inhibitors, are there other reports and could that also be in consideration as we discuss the label.

DR. SILVERSTEIN: I didn't catch the end of that comment so I apologize. The ACE inhibitor is definitely in the label that is contraindicated. It is in the label for FH and it is in the label for the FSGS so that is a well-known complication. We, unfortunately, do see this time to time where patients are given an ACE inhibitor on the same day. It is probably related to maybe being treated in one place and getting therapy in another place. It is probably just a lack of communication. It probably would be beneficial if every patient is asked before they go on the therapy if they took an ACE inhibitor on that day or if the parents are asked,

in the case of children. I think that probably would be worthwhile. I think that is probably being done. We can certainly assess whether that is being done on a regular basis. But it does happen occasionally. Again, this didn't happen in the study, it happened outside the study but the point of when patients come in to get a therapy their medications should be reviewed. Not only their typical medication list but also what medications they took that day, so we can maybe reiterate that.

DR. HUDAK: Dr. Turer.

DR. TURER: Christy Turer. The last time this was presented I had asked a question about whether weight was being measured in part because FSGS can be a mixed bag. In adults, we know that there is, well we believe there is an entity called obesity related glomerulopathy. So my first question is, has weight been assessed in these kids.

The second one is, how is GFR being measured because in adults we measure GFR

differently than we do in kids. Depending on whether you use the Schwartz-Lyon formula and you use standard versus adjustment for ideal body weight or true BSA using real body weight could alter the way in which EGFR is estimated.

DR. SILVERSTEIN: Yes I remember that comment from last year. Weight is being recorded. Right now, I think what you're talking about is the etiology of FSGS as opposed to -- and so on large scale studies it has been shown that some patients with obesity are more prone to developing FSGS. For the purpose of this particular study, we only have eight patients so we don't really have that data to report right now because we have a very, very small sample set. But that relationship of obesity in FSGS and there are well-known mechanisms now that have been unearthed, does exist for children. But for this particular study, only eight patients, there wasn't much to assess.

Your second point about GFR, in pediatrics we used to use what was called the

Schwartz formula now we use the modified Schwartz formula using the 0.413 as the denominator and that is basically what is being used. So you have a serum creatinine, you plug it in to a formula using the patient's height in centimeters, divide that 0.413 and you get the GFR. That's how it is being done in standard ways.

Now, to your point, I think about can this underestimate or overestimate or give you an improper result for patients who are malnourished, et cetera. That certainly is a problem, we know that. That is a limitation of using serum creatinine for any measure of GFR because of the possibility of malnourishment. But I think for the patients in the study, unless there was a drastic change in their nutritional status throughout the study I don't think it would affect the longitudinal assessment of GFR. Does that answer your question?

So if their GFR is lower, is artificially high in the beginning because they are malnourished, it is probably not going to

change drastically throughout the study. So the GFR is going to be similarly affected throughout the study. But we know on a point by point basis, GFR can certainly be overestimated in a patient who is malnourished if you're using serum creatinine. If you did a cross-sectional look at a patient population you're going to get some who are going to fall into that. But if you look into a longitudinal study over a three to six month period of time I would be surprised if the serum creatinine is going to change drastically because of nutritional status.

DR. PEIRIS: And perhaps you want to clarify the question also related to obesity. Your concern, I'm assuming, is just adiposity because these patients certainly have extravascular fluid volume issues that can alter our ability to be accurate about lean body mass, lean muscle mass and what Doug is bringing up as well is that issue with respect to nutritional status correlated with lean muscle mass, correlated with creatinine and then how that is

evaluated as a factor in the GFR measurement. I just want to help clarify the discussion because there is a few points that are being thrown around here that are not clear.

DR. HUDAK: Dr. Kaskel.

DR. KASKEL: Rick Kaskel. So when the patients, few numbers, that had a remission is certainly encouraging because we know usually the unremitting course of these children and adolescents with nephrotic syndrome does not respond to anything is loss of renal function within two to five years and they are in dialysis mode. So short term data shows that about three of them have gone into a full remission, a couple have a partial remission, that is very encouraging. Has any thought been given to possibly giving those that have a remission another treatment with either another immunosuppressive agent down the line if they relapse, or is there any thought about recurrent use of this treatment in the future if someone goes in remission and then relapses.

DR. SILVERSTEIN: Good question. So that usually means I don't have an answer. It is a very, very good question because we know that patients who have FSGS and nephrotic syndrome, once they stop responding to one drug they're going to stop responding to others. It sort of becomes a rolling ball down the hill.

So if they are steroid responsive which is a typical drug given to most patients with nephrotic syndrome, if they are initially steroid responsive and then they become steroid resistant, they may be responsive initially to the next drug. But if you are initially steroid resistant you are probably not going to respond to anything. You might get a little bit of a response to another drug.

So the question you're asking is, they finished the study, now they're out, now what happens to them. And so what the doctors decide to do outside the study is not under our purview, however, I would think if the patients went into remission and they still had a catheter, the

question is, personally what I would do, I would leave the catheter in for a while and see how the patient does after the treatments are done. But again, these patients are getting three to six months follow up after their last treatment but I would consider leaving it in. I would also say to myself, they responded to this, what does that mean. Could I reintroduce a drug like cyclosporine again and try that, I certainly would.

I think that as all the nephrologists here know, that you get to a point of diminishing returns as the GFR declines and you get to the point where you say to yourself, I'm just throwing more immunosuppression at the patient, I'm adding on adverse events when I can already see where this is going. So I think that's a decision that people would have to make depending upon the GFR. If their GFR at the end of the study is lower and is now 50, 40, 30, I'm starting to say to myself, I don't want to give up on the patient but I might be at that point where any therapy I might provide

might tip the scales for risk greater than benefit. And we all go through that decision making and we have those discussions with families and you have to make a decision together and think about where you want to go.

We know the patients who get plasmapheresis for recurrent FSGS after kidney transplantation. The success rate has been shown to be over the years to be relatively good. So it is a similar type therapy to this device and it is probably going to be relatively similar in efficacy and risk as time bears out. But the point I was going to make, is we know that some of those patients have to be cycled through again. They develop recurrence, they get treated, they get better and then six months to a year later they have another episode of recurrence. And recurrence is obviously specifically defined for patients after kidney transplantation.

So I would think that another course of therapy depending how the patient did would be something as a consideration but certainly

wouldn't leap into that without a lot of thought or maybe a reintroduction of a drug. So, you're right. What do you do with these patients after this. This is the classic question we have with patients with FSGS. Because if you don't do anything and the patient doesn't improve they end up getting a kidney transplant and then they're exposed to different types of medications and different types of risks. Transplantation is better than dialysis, we all know that, but at the same time, there are risks involved. So long answer, I don't know if I answered your question but I think it depends on a lot of factors.

DR. HUDAK: Another question.

DR. KASKEL: Rick Kaskel. Why was an adult on dialysis given this treatment on the same day once they reached end stage?

DR. SILVERSTEIN: Good question. We don't know. We don't know the details of that. The MDR reports just give you certain amounts of information. I personally would not, obviously that was somebody who -- well, very, very, likely,

that is somebody who had FSGS and it is theoretically possible the patient reached hemodialysis for a reason other than FSGS. But presuming it was FSGS and that's why they were receiving Liposorber therapy, I'm not really sure why you would do that on the same day. If I'm giving a patient hemodialysis, the only other possibility is the patient had familial hypercholesterolemia and also had renal failure for another reason.

DR. KASKEL: Is it worth making a comment that we would not recommend using it in a pediatric patient who reaches end stage?

DR. SILVERSTEIN: Well you couldn't, the way the indications for use are is you have to have a GFR of 60 or greater. So that eliminates that possibility. But your point comes back to the point that I think has been made before about does the labeling need to indicate that if you're receiving another extracorporeal therapy on that same day and/or they is hemodynamic compromise for other reasons that you may want to hold off

Liposorber therapy. There is no emergency to do Liposorber therapy.

So what I would have done in that patient, let's say the patient had FH and also developed renal disease for some other reason and was on an end stage and was getting dialysis. I'll give the dialysis and I wait a couple of days and once the patient is recovered I look at my window to use Liposorber therapy. The emergent treatment there is not in Liposorber therapy it is hemodialysis. I am just suspicious there was a disjointed type of care. One group was giving one therapy, one group was giving another therapy. I have to believe that that was a significant possibility.

DR. HUDAK: Thank you, Dr. Silverstein, that was a great discussion. I think we've come to the end of the discussion. So we can bring up the slide on the recommendations. We'll do an electronic vote on this. Oral votes, we'll start with you, Dr. Kishnani.

DR. KISHNANI: I concur, just with the

one thought that I had mentioned earlier if somewhere it can be stated about the caution with hemodialysis use around the same day and also the same for the ACE inhibitor. I know that is already in the label but I don't know if there is another way to reemphasize it. Overall, I concur.

DR. HUDAK: Okay and we'll start with Dr. Cnaan.

DR. CNAAN: Avital Cnaan, I concur.

DR. ZUPPA: Athena Zuppa, I concur.

DR. CALLAHAN: David Callahan, I concur.

DR. WHITE: Michael White, agree.

MS. MOORE: Erin Moore, concur.

DR. CATALETTO: Mary Cataletto, concur.

DR. WADE: Kelly Wade, concur.

DR. ANNE: Premchand Anne, concur.

DR. KASKEL: Rick Kaskel, I concur.

DR. SAYEJ: Wael Sayej, I concur.

DR. TURER: Christy Turer, I concur.

DR. HUDAK: Very good. The CDRH rates, you've had three unanimous votes so you've done well for the day. So we have reached the end of

the program and I'll leave it to Marieann to make any administrative comments at this point.

MS. BRILL: For your reimbursements, Euneka will be sending an email within a week so please make sure that you returned or you respond to Euneka’s email. Thank you.

DR. HUDAK: Just another reminder to turn in the discs before you leave if you have them. All right, we're adjourned, thank you.

(Whereupon, at 11:39 a.m., the PROCEEDINGS were adjourned)

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CERTIFICATE OF NOTARY PUBLIC

COMMONWEALTH OF VIRGINIA

I, Carleton J. Anderson, III, notary public in and for the Commonwealth of Virginia, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

(Signature and Seal on File)

Notary Public, in and for the Commonwealth of Virginia

My Commission Expires: November 30, 2020

Notary Public Number 351998