UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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Office of the Commissioner

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PEDIATRIC ADVISORY COMMITTEE (PAC)

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Via Web Conference

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Participants

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Chairperson	Gwenyth Fischer, M.D.
Pediatric Advisory Committee Member	Premchand Anne, MD, MBA, MPH
Pediatric Advisory Committee Member	Susan S. Baker, MD, PhD
Pediatric Advisory Committee Member	Douglas Diekema, MD, MPH
Pediatric Health Organization Representative (non-voting)	Jennifer Goldman, MD, MS
Pediatric Advisory Committee Member	Charleta Guillory, MD, MPH
Pediatric Advisory Committee Member	K. Sarah Hoehn, MD, MBe
Pediatric Advisory Committee Member	Richard Holubkov, PhD
Pediatric Advisory Committee Member	Liza-Marie Johnson, MD, MPH, MSB
Patient-Family Representative	Gianna McMillan, DBe, MFA
Industry Representative (non-voting)	Robert Nelson, MD, PhD
Pediatric Advisory Committee Member	Roberto Ortiz-Aguayo, MD, MMM
Consumer Representative	Randi Oster, MBA
FDA Participant	Denece Clayborne, RN, MSN
FDA Participant	Scott Colburn, MS, BSN, RN
FDA Participant	Dionna Green, MD, FCP
FDA Participant	Charu Gupta, MD (MBBS), MPH
FDA Participant	Ivone Kim, MD
FDA Participant	Colin O'Neill, MBE
FDA Participant	Craig Zinderman, MD, MPH

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Call to Order

Dr. Fischer: Good morning, everyone, and welcome today's meeting of the Pediatric Advisory Committee. I'd like to just remind everyone right now to please mute yourselves on the Zoom platform and also on any telephone lines when you are not speaking today. For Media and Press, we have a new contact address for you. It's under the U.S. Department of Health and Human Services Press Room listed here. Their website, as you can see here is hhs.gov/press-room/index.html. The phone number that you can reach them at is 202-690-6343. For members of the Open Public Hearing industry and press, please sign in by sending an email to PAC@fda.hhs.gov. And if you're having any technical issues or you have technical inquiries, contact the AV Support Team at virtual-WOCC-Support@fda.hhs.gov as listed on this slide. Next slide, please. This slide displays the icon accessible for closed captioning today. Okay, next slide, please.

Good morning, everyone. My name is Gwenyth Fischer. I'll be chairing today's virtual meeting. I will now call today's meeting at the Pediatric Advisory Committee to order. The FDA has convened today's meeting to discuss the post-marketing pediatric-focused safety reviews that FDA has completed for several products across the three medical product centers. The Center for Drug Evaluation and Research, known as CDER, the Center for Biologics Evaluation and Research known as CBER and the Center for Devices and Radiological Health, known as CDRH. The FDA's review of adverse event reports for the products under discussion today did not identify any new pediatric safety concerns. Therefore, no product specific presentations will be made by the FDA or industry. PAC members received FDA's review documents in advance of today's meeting to become familiar with the adverse events that were reported for these products and FDA's assessment of these events. The PAC will have the opportunity to ask the Agency clarifying questions during this meeting. Following a Question-and-Answer session and Committee discussion, the PAC will convey their recommendations for safety monitoring of these products via a vote. I would like to remind the Committee that the scope of today's discussion will be

limited to post-marketing safety and surveillance activities as reflected in the Agency's review documents. Other matters pertaining to the use of products under discussion such as general development questions are outside of today's scope. Our goal is that today's meeting will be a fair and open forum for discussion of the planned topic, ensuring individuals can express their views without interruption. With that said, if the discussion veers towards topics beyond the stated scope of the meeting, I may as Chairperson refocus the discussion as needed. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by myself.

We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the Open Forum of the meeting. We are aware that members of the media may be anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until it is concluded. Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you, everybody. On behalf of the FDA, I want to thank all of the Committee members for their participation today. Next slide.

Introduction of the Committee

Dr. Fischer: We'll start by going over today's meeting roster. I ask all members of the Committee to turn on their cameras now and keep them on for the duration of roll call. When I call your name, please briefly introduce yourself with your primary area of expertise, your institutional affiliation, and the role that you have on this panel. I'll begin by introducing myself. My name is Dr. Gwenyth Fischer. I'm a pediatric critical care and medical device specialist. I'm an Associate Professor of Pediatric Critical Care and the Division Director of Pediatric Critical Care at the University of Minnesota, and also the Associate Director of the Medical Device Center at the University of Minnesota. I also direct the Pediatric Device

Innovation Consortium at the University of Minnesota. I'm also the Chair of this Committee. Next, we have Premchand Anne.

Dr. Anne: Hi, there. I'm Premchand Anne. I'm the Director of Pediatric Cardiology, Director of Adult and Pediatric Lipid Clinics, as well as the Director of the Pediatric Residency Program here at Henry Ford St. John Children's Hospital in Detroit. I'm also a Clinical Associate Professor of Internal Medicine Pediatrics at Wayne State University. Thank you.

Dr. Fischer: Thank you. Susan Baker.

Dr. Baker: I'm Susan Baker. I'm Professor of Pediatrics at the University at Buffalo. My specialty is gastroenterology. I was formerly the Division Director, the Training Program Director and had served on many other Committees. Thank you.

Dr. Fischer: Thank you. Douglas Diekema.

Dr. Diekema: Good morning. I'm Doug Diekema. I am a Professor of Pediatrics at the University of Washington and the Director of Education at the Treuman Katz Center for Pediatric Bioethics as part of Seattle Children's, and I am a standing member of the Pediatric Advisory Committee.

Dr. Fischer: Thank you. Jennifer Goldman.

Dr. Goldman: Morning. Jennifer Goldman. I'm a Professor of Pediatrics at Children's Mercy in Kansas City. My specialties are pediatric infectious diseases and clinical pharmacology, and I serve as the Pediatric Health Organization Representative.

Dr. Fischer: Thanks. Charleta Guillory.

Dr. Guillory: Good morning. My name is Charleta Guillory and I am a Professor of Pediatrics in the Division of Neonatology at Baylor College of Medicine. I'm Director of the Neonatal-Perinatal Public

Health Program at Texas Children's Hospital. In addition, I serve as the state Perinatal Quality Collaborative for the state of Texas. Thank you.

Dr. Fischer: Thank you. Sarah Hoehn.

Dr. Hoehn: Thank you. I'm Sarah Hoehn. My areas of expertise are pediatric critical care medicine, pediatric ethics, pediatric hospice and palliative care. I am the Chief Medical Officer of La Rabida Children's Hospital, and I'm a Clinical Associate at University of Chicago Comer Children's Hospital. Oh, and sorry, I'm an ad hoc member of the Pediatric Advisory Committee.

Dr. Fischer: Thank you, Dr. Hoehn. Richard Holubkov.

Dr. Holubkov: Oh, hi. Rich Holubkov. I'm sorry, just to AV, it says my video is disabled by the host. I'm a standing member of the Committee. I am a Clinical Trialist Biostatistician based at the Data Coordinating Center at the University of Utah School of Medicine.

Dr. Fischer: Thank you. Liza-Marie Johnson.

Dr. Johnson: Good morning. I'm Dr. Liza Johnson. I'm an Associate Professor in the Department of Oncology at St. Jude Children's Research Hospital and Director of the Bioethics Program. Thank you. Oh, and an ad hoc member.

Dr. Fischer: Gianna McMillan.

Dr. McMillan: Hi, I am Dr. Gigi McMillan. I have recently retired from Loyola Marymount University. I'm a bioethicist and a longtime Family-- Representative Family Advocate. Currently, I'm the Chair of the Board for PRIM&R on Public Responsibility in Medicine and Research.

Dr. Fischer: Robert Nelson. Oh, we can't hear you, Dr. Nelson. You're muted.

Dr. Nelson: Yep. Thanks, I got the prompt. Sorry. I'm Dr. Robert Nelson. I'm currently the Executive Director of Pediatric Drug Development at Johnson & Johnson. My clinical specialties are neonatology and pediatric critical care, and I am the Industry Representative on the Pediatric Advisory Committee.

Dr. Fischer: Thank you. Roberto Ortiz-Aguayo.

Dr. Ortiz-Aguayo: Hi, Roberto Ortiz-Aguayo. I'm a pediatrician and a child psychiatrist with expertise in complex pharmacology in patients with comorbid physical and concurrent behavioral disorders, and I'm a Chief of Psychiatry at the Nemours Children's Health and an Associate Professor of Psychiatry and Pediatrics at Thomas Jefferson University.

Dr. Fischer: Great. And Randi Oster.

Ms. Oster: Yes. Hi, I'm Randi Oster. I am a Consumer Representative with My Medi Benefits and I help consumers navigate the healthcare system.

Dr. Fischer: Thank you, Randi. And thank you, everyone, for joining us today and sharing your expertise with the PAC Committee. I'm now going to pass the meeting on to Shivana Srivastava to announce the FDA Representatives who are joining us for today's meeting. Next slide, please.

Ms. Srivastava: Hello, my name is Shivana Srivastava and I'm the Designated Federal Officer for today's meeting. In today's meeting, FDA speakers will be Dr. Dionna Green from the Office of Pediatric Therapeutics, Mr. Scott Colburn from CDRH, Dr. Craig Zinderman from CBER, and Dr. Ivone Kim from CDER. They will briefly introduce themselves when they address the Committee. Additional FDA participants and representatives will introduce themselves when speaking throughout the meeting. I will now read the Conflict of Interest Statement. Next slide.

Conflict of Interest Statement

Ms. Srivastava: The Food and Drug Administration is convening today, July 9th, 2025, for a meeting of the Pediatric Advisory Committee under the authority of the Best Pharmaceuticals for Children Act of 2002, the Pediatric Research Equity Act of 2003, the Food and Drug Administration Amendments Act of 2007, the Food and Drug Administration Safety and Innovation Act of 2012 and the Federal Advisory Committee Act of 1972. This meeting is a particular matter involving specific parties, products, devices and biologics for which the Committee will discuss post-marketing safety events reported for these products. With the exception of the Industry Representative, all standing members of the Committee are special government employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC § 208 is being provided to participants at this meeting and to the public. Related to the discussions of today's meeting, standing members and temporary voting members of the Committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for the purposes of 18 USC § 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. This may include interests that are current or under negotiation. No regular government employees were added to the Committee for this meeting. Therefore, the conflicts of interest screening was limited to standing members and temporary voting members of the PAC. FDA has determined that the members of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC § 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual services outweighs his or her potential financial conflict of interest, or when the interest of a regular government

employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee. Based on the agenda for today's session and all financial interest reported by the Committee members, no conflict of interest waivers have been issued for this meeting.

With respect to the meeting's Consumer Representative, we would like to disclose that Ms. Randi Oster is participating as a Voting Representative, acting on behalf of consumers, not on behalf of any organization, company, or product. With respect to the meeting's Patient Representative, we would like to disclose that Dr. Gianna McMillan is participating as a Voting Representative, acting on behalf of patients, not on behalf of any organization, company or product. The Consumer and Patient Representatives are special government employees and as such have been screened for conflicts of interest. With respect to the meeting, Dr. Jennifer Goldman is participating in this meeting as the Pediatric Health Organization Representative and that is a non-voting position. With respect to FDA's invited Industry Representative, we would like to disclose that Dr. Robert Nelson is participating in this meeting as a Non-Voting Representative acting on behalf of regulated industry. This Representative is not a regular special government employee and has not been screened for conflicts of interest. Dr. Nelson's role at this meeting is to represent industry in general and not any company. Dr. Nelson is employed by a firm that has a product that is coming before the Committee. In accordance with our regulations at 21 CFR § 14.86(c)(4), Dr. Nelson has been reminded that an Industry Representative may be present at a meeting even if a product sponsored by his employer or its subsidiary is coming before the Committee. However, his role as an Industry Representative is to represent all of industry and not any specific firm or product. Consistent with Commissioner Makary’s April 17, 2025, statement, FDA's only including Industry Representatives in Advisory Committee meetings where required by statute. FDA is required to include an Industry Representative in today's meeting under 21 U.S.C. § 355(n)(3)(C). Under FDA regulations, although a non-voting member serves in a representative capacity, the non-voting member shall exercise

restraint in performing such functions and may not engage in unseemly advocacy or attempt to exert undue influence over the other members of the Committee.

FDA encourages all meeting participants, including the Industry Representative and Open Public Hearing speakers to advise the Committee of any financial relationships that they have with any affected firms, its products, and if known, its direct competitors. We would like to remind the members that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. To ensure transparency, we encourage all standing Committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. We would like to remind members that if the discussions involve any other firms or products not already on the agenda for which a PAC member has a personal or imputed financial interest, the participant will need to exclude themselves from such discussion and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial relationships that they may have regarding the topics that could be affected by the Committee's discussions. Thank you. I'll now turn the meeting back to our Chair. Next slide.

FDA Opening Remarks

Dr. Fischer: All right. We will now proceed with Opening Remarks from Dr. Dionna Green, Director of the Office of Pediatric Therapeutics.

Dr. Green: Thank you, Dr. Fischer. Good morning, everyone. I would like to welcome our Committee members and guests who are joining us for today's Pediatric Advisory Committee meeting. I want to start by first thanking our Committee members for their service and for the time you have taken to review the advanced materials and to prepare for today's meeting. I would also like to thank the following groups. The FDA staff who performed or contributed to the pediatric-focused post-market safety reviews

that are the subject of today's meeting. I would also like to thank the FDA staff members who are participating today and all who have contributed to the logistics and planning for the meeting. We also want to thank the AV staff for all of their technical support today. And last but not least, we want to thank the public for joining us today for our meeting. Next slide, please.

At today's meeting, the Pediatric Advisory Committee is convened to discuss pediatric-focused post-market safety reviews as mandated by the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act, and the Pediatric Medical Device Safety and Improvement Act. Next slide. Before we proceed with the focus of today's meeting, I will first provide an update on the Pediatric Research Equity Act Non-Compliance Letters as required by legislation. FDA issues PREA Non-Compliance Letters to sponsors if they have failed to submit within the timeframe a required pediatric assessment or report of a molecularly-targeted pediatric cancer investigation as appropriate. FDA has also issued such a letter if a sponsor failed to request approval for a pediatric formulation as described in section 505(b) of the Food Drug and Cosmetic Act. Consistent with the Act, FDA has also made publicly available on the FDA website the PREA Non-Compliance Letter and sponsor's response with certain redactions. If a sponsor has requested a deferral extension or submitted a waiver request by the due date of the pediatric assessment or the report of the molecularly-targeted pediatric cancer investigation, FDA has not issued a PREA Non-Compliance Letter unless FDA subsequently denied the deferral extension or waiver request. Next slide.

So, since the last reporting on the Non-Compliance Letters at the September 2024 Pediatric Advisory Committee meeting, there has been one new letter issued by CBER, the Center for Biologics Evaluation and Research. Next slide. And there have been 15 new letters issued by CDER, the Center for Drug Evaluation and Research. The information related to these letters are listed on the previous slide, this slide and the following slide, and can also be found on FDA's website. Next slide. Next slide. So, now in terms of the agenda for today's meeting, the meeting will proceed as follows. We will first have an Open Public Hearing beginning at 10:30 a.m. eastern. At 11:30 a.m., there will be a listing and discussion

of the products evaluated in the pediatric-focused post-market safety reviews completed by CDRH, the Center for Devices and Radiological Health. This will be followed by a listing and discussion of the products evaluated by CBER. There will be a lunch break that is scheduled for approximately 1:00 p.m., and the meeting will resume at 1:30 p.m. for a listing and discussion of the products evaluated and the pediatric-focused post-market safety reviews completed by CDER. There is time allotted for clarifying questions and voting at specified times during the meeting. We are scheduled to adjourn the meeting at approximately 3:30 p.m. However, please note that depending on the pace of the meeting and how it proceeds, it is possible that all of these times may shift. Next slide.

During today's meeting, there will be three separate voting sessions, one each for CDRH, CBER and CDER. The voting question and response choices will be the same for all centers and all products that are discussed today. Voting by the Pediatric Advisory Committee will occur via the Zoom platform. A separate ballot will be launched for each Center's vote and will contain a series of the same voting question, one for each of the products listed on the ballot. Please note that for certain CDER products they were grouped into the same pediatric-focused post-market safety review, and therefore those products will be grouped for voting purposes as well. Next slide.

As was previously mentioned, FDA's review of adverse event reports for the products under discussion today did not identify any new pediatric safety concerns. Therefore, the Voting Question for each product is as follows. "The FDA recommends continuing routine, ongoing post-market safety monitoring of each of the CDER, CDRH or CBER products under discussion. Does the Pediatric Advisory Committee concur?" Voting members of the Pediatric Advisory Committee can vote "Yes, routine ongoing post-market monitoring should continue" or vote "No, additional evaluation or surveillance should be considered." Voting members can also choose to abstain from voting and some voting members will be recused from voting on certain products due to conflicts of interest. Next slide.

Meeting attendees trying to join the meeting during the time of voting or vote tabulation will be placed in a waiting room until the meeting resumes. Once the meeting resumes, the voting results will be displayed and read into the record by the Designated Federal Officer, following which each voting member of the Pediatric Advisory Committee will be called upon to state their individual vote for the record. Next slide. Thank you for your attention and I will now turn the meeting back to our Chairperson, Dr. Fischer.

Open Public Hearing

Dr. Fischer: Thank you, Dr. Green, for your presentation. We can go to the next slide. Okay. We are going to open the Public Hearing session now. Welcome to the Open Public Hearing. If you wish to speak, please state your name and your affiliation if it's relevant to this meeting.

The Food and Drug Administration believes that the Agency and the public benefit from a transparent process that helps ensure the FDA decisions are well-informed by the advice and information FDA receives from its Advisory Committees. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, with its product, or if known, any of its direct competitors. For example, this financial information may include a company's or group's payment for your travel, lodging or other expenses in connection with your attendance at this meeting, or grant money that your organization receives from the sponsor or a competitor. Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships to which you may state for the record. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this Committee place great importance in the Open Public Hearing process. The insights and comments

provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this Open Public Hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the Chairperson. Thank you for your cooperation.

We do not have any pre-registered speakers, I believe. So, if at this time any member of the public wishes to speak, please raise your hand. Let's see. Anybody? Okay, so if we do not have anyone who wishes to speak at this moment, then we will continue with the meeting. If you do wish to speak, please email PAC@fda.hhs.gov and let our team know that you wish to speak and we will be circling back on the Open Public Hearing in another 15 minutes. So, the Open Public Hearing will be open until 11:30.

Listing of products evaluated in the pediatric-focused post-market safety reviews completed by the Center for Devices and Radiological Health (CDRH)

Dr. Fischer: We're going to now continue with today's meeting agenda, and we're going to transition to the discussion about pediatric-focused post-market safety reviews completed by the Center for Devices and Radiological Health represented by Mr. Scott Colburn.

Mr. Colburn: Thank you, Dr. Fischer, and good morning to everyone in attendance, and also a thank you to our esteemed panel members and FDA colleagues for their service and commitment to today's very important event. For the record, my name is Scott Colburn. I serve as the Director of the Office of Readiness and Response within the Office of Strategic Partnerships and Technology Innovation in CDRH at FDA. I will now read the list of CDRH regulated devices that are under discussion at today's meeting. Our first device is the LIPOSORBER LA-15 System, followed by the Medtronic Activa Neurostimulator for Dystonia Treatment, the Minimally Invasive Deformity Correction or MID-C system, the REFLECT

Scoliosis Correction System, and finally the Tether-Vertebral Body Tethering System. Thank you. I'll now transition the meeting back to Dr. Fischer our PAC Chairperson.

Clarifying Questions

Dr. Fischer: Thank you, Mr. Colburn. Okay, well we will now proceed with any clarifying questions from the PAC. I'll remind you to use the “Raise your hand" button so that I know whether or not to call on you. When called upon, please remember to state your name for the record before asking your question. Please just ask one question at a time. If you have multiple questions, we will circle back on you if time allows. We will begin with individuals who submitted questions to the Agency in advance of the meeting. When I call your name, please read the question into the record. If you submitted multiple questions, again, I'll just ask you to start with your first question and then again, we will get to other questions as we have time. So, I believe our first question was from Randi Oster. Randi, if you'd like to speak now, go ahead.

Ms. Oster: Yes, thank you. In 2024, there were over two million adverse events reported to FAERS. And then from a safety perspective, airlines try to strive for Six Sigma, that's 3.4 adverse events per million opportunities. With this many adverse events, we would need 588 billion opportunities to feel safe as the airlines. Therefore, my first question on the first drug has to do with the fact that subjects withdrew without follow-up, and I want to understand on a go-forward basis what incentive can be provided to help individuals understand that their experience is valuable. And then we also had people limited by protocol deviation. How do we prevent that from happening on a go-forward basis?

Mr. Colburn: Thank you, Randi. I just wanted to ask for clarification which device you are referring this question to so that way I can make sure we direct it appropriately.

Ms. Oster: First one up is the LIPOSORBER.

Mr. Colburn: Okay, thank you very much. I will ask Dr. Charu Gupta to come up and help answer that question. I appreciate it.

Dr. Gupta: Thank you. Hi, everybody. Thank you for the question. My name is Charu Gupta, I'm a pediatric nephrologist. I work with the renal and transplant devices team here at CDRH. So, to answer your question with regards to protocol deviations and also patient withdrawals, we completely shared and acknowledge your concern with regards to retaining patients as much as possible and minimizing protocol deviations as much as possible within any clinical study. However, as you know, there could be several potential reasons for why patients may not return for follow-up visits, including the overall toll of the disease itself or the treatment especially with this system. And additionally, the follow-up period for this study is rather long. However, as part of conditions of approval for this device, the sponsor is required to successfully complete this post-approval study, and when withdrawals do happen or protocol deviations do happen, that data is lost and there is also a reduced reliability of the data that is available for us to review. And therefore, the sponsors are actually generally speaking very motivated to ensure good follow-ups and to minimize protocol deviations. To that end, the sponsor for this system does have certain measures and best practices built into the post-approval study protocol to retain patients in the study. And as far as the protocol deviations are concerned, these protocols are meant for physicians and other study staff who conduct these studies, and these professionals are highly trained individuals, so for example, pediatric nephrologists in this case. Additionally, the study protocol does require these principal investigators to sign a document stating that they agree to comply with the terms of the protocol, meaning they will follow the protocol as documented. Overall, I wish to assure you that we, as FDA, are committed to guide the sponsors for successful study completion, and in our future interactions with the sponsor, we will continue to emphasize and highlight issues related to increased patient retention withdrawal as well as protocol deviations. Thank you. Is there anything else I can answer for you?

Ms. Oster: No. Thank you very much.

Dr. Gupta: Thank you.

Dr. Fischer: Thank you, Randi. I believe we had a question submitted ahead of time by Dr. Hoehn as well. Dr. Hoehn, if you'd like to speak now.

Dr. Hoehn: Thank you. Sarah Hoehn. I'll direct my first question to the Tether-Vertebral Body Tethering System. And my question is about on table nine, which was on page 25 of the Tether System, which is that-- My question was about the nine events of a broken tether. That seems like a high rate of mechanical failure, so I wanted some clarity on that particular information.

Mr. Colburn: All right, thank you for your question and we just happen to have an expert from that group, Mr. Colin O'Neill, and I'll ask him to come to the podium. Thank you.

Mr. O'Neill: Thanks Scott and thank you Sarah for the question. My name's Colin O'Neill. I'm an Assistant Director in the Division of Spine Devices in the Office of Orthopedics in CDRH. It's a good question, and I want to give some context to these types of surgeries that apply to the tethers and the MID-C device. Specifically, pediatric tether devices provide a lateral tension band across the convex side of the spine, and in the case of the MID-C, a brace on the concave side of the spine. Device insertion and tensioning partially corrects the curvature and the remaining spinal growth can provide additional correction. Device breakage does not necessarily mean that the procedure was unsuccessful. Tethering of the spine during the time between tether insertion and subsequent surgery can provide adequate curve correction to avoid the need for fusion surgery, and that's key. Re-operations and subsequent surgical interventions do not necessarily mean the patient will require a fusion, and the ultimate success of a procedure is judged by whether or not the patient is able to avoid spinal fusion if the patient finishes growing and has a curve or a Cobb angle equal or less than approximately 40 degrees. So, a cord breakage is a radiographic finding that may not be clinically considered a failure and may not have

clinical significance. For example, sometimes a tether breakage is good if overcorrection is occurring and there are procedures done to cut tethers in cases of overcorrection. I hope that answers the question.

Dr. Hoehn: Thank you. May I ask a follow-up question only since you mentioned the other device as well, because I also had a similar tether question on the REFLECT scoliosis. Would the same thing that you just said be true that the goal is to avoid the spinal fusion, so if the tether doesn't work, that's okay because it still meant it achieved the greater goal.

Mr. O'Neill: Yeah, so, the goal is to delay or ultimately avoid fusion, and this is an elective surgery, so there's a lot of patient preference elements that go into this decision-making. And the tethering devices follow the general concept in orthopedics of not fusing but allowing motion where that was the natural intent of those joints in the spine as well. And when you introduce also the growing spine in skeletally immature patients, the preference to avoid a fusion that can have long-term clinical sequelae is what this procedure is going for. So, I know sponsors are aware of, and investigating, and looking at tether breakages, and it does occur, it's not always a bad thing and we're aware of these adverse event rates that are expected and align with the study data that supported the original HDE approval. Does that answer your question?

Dr. Hoehn: Yes, it does. Thank you.

Dr. Fischer: Thank you. And this is Gwenyth Fischer. I have a general question, but I'll direct it specifically at the Activa Neurostimulator. I'm curious from the FDA's perspective whether you feel that you get accurate UDI data, Unique Device Identifier data, and whether or not that's an area for improvement for hospitals and others to make sure that you're getting specifically information on individual device data, not just-- I’m using that as an example, but as a more general question as well.

Mr. Colburn: Thank you, Dr. Fischer. What I'll do here is see if we can have Ms. Denece Clayborne from that Division be able to try to answer that, so to get more specific to that type of device area, and I'll follow up on anything else after. Denece, are you able to come off mute? She's joining us virtually.

Ms. Clayborne: Hello. Can you hear me okay?

Mr. Colburn: Yes.

Ms. Clayborne: This question was in regard to the cords or did I miss--?

Dr. Fischer: The question is regarding specifically the neurostimulator, but it's more of a general question I have for the FDA about whether they feel that the data they get on UDI, Unique Device Identifiers, across products is accurate and whether or not they feel like they're getting sufficient data from hospitals across the board.

Ms. Clayborne: Oh, okay, I understand. Yeah, so for UDI, that information is in the medical device reports [MDR] that we receive. Since they have made it mandatory for the manufacturers to provide that information, the MDRs that we receive from manufacturers do include that information. We oftentimes can go back and ask them if it is missing for some reason. As far as voluntary reports, sometimes that information is not included, or typically is not included, depending on how much information is provided. And depending on if the voluntary reporter is allowing us to contact them, we may or may not be able to receive that UDI information.

Dr. Fischer: Thank you. Just thinking that's an opportunity on the hospital side to improve reporting. Other questions? I don't see any other hands raised, but Randi, I believe that you submitted a couple of additional questions if you'd like to go ahead.

Ms. Oster: Yes, thank you. And just going forward, I'd like us to stay forward on one drug or one device at a time. So, I will go back to the tether question and then I will do the Activa question. And on

the tether, I understand that breakage is not necessarily a bad thing. However, we had over 86% of the reports that were deleted, and it just is not clear if they're coming in as serious events and then we're saying it was an expected event. How do we go forward in additional studies going forward to really separate out what you've already described as “not serious” when it comes in as “serious”?

Mr. Colburn: All right, I'll ask Colin to come up and continue that. Thank you.

Mr. O'Neill: Yeah, so my understanding of the categorization of cord breakages is it’s there are re-operations that are expected with this type of treatment. So, when a cord breaks, not in the case of overcorrection, or when inadequate correction happens, there's an expectation that a re-operation could occur. And that's all within the overall goal of trying to avoid a fusion with these repeated operations. There are many avenues that we track these events: through MedWatch, through annual reports, HDE annual reports from the sponsor, and also study groups like the Harms Study Group. So, we're actively engaged in understanding the context and the importance of tracking these cord breakages. But yeah, my understanding is it has occurred especially early on in the technology and it's actively being addressed.

Ms. Oster: And as a follow-up to that, are we tracking it by physician? Are we starting to see that maybe there are physicians that have lessons learned that they could be repeating? And also, is it typically new physicians using this, and there is an opportunity that as there is more experience we can reduce this?

Mr. O'Neill: Yeah, my understanding is it's a small community of surgeons in relatively few institutions that provide this treatment, and best practices are continually shared from in these surgical communities by publishing case studies as well as prospective and retrospective data from surgeons that have experience with these devices.

Ms. Oster: And then my last question is: you mentioned MedWatch. Well, we did not get any data about MedWatch. How many reports did you have from MedWatch?

Mr. O'Neill: I don't have that information readily available in my notes, but I did want to add a little bit of detail to the previous answer. Surgical techniques on the amount of correction and the tension that is initially put on these tethers and force put on these devices to obtain initial correction is an important consideration, and the sponsors are aware of this and have provided surgical instruments to assist with measuring the tension intraoperatively to hopefully prevent these breakages. In terms of MDRs, I don't have the-- I think it's in the Executive Summary that information is available and that was as of the data cut off for this presentation, which was months ago.

Ms. Oster: Thank you.

Dr. Fischer: Mr. Colburn, I'm going to go ahead and close the Open Public Hearing here as we have not had any further requests to speak to the FDA. So, thank you everyone. And then Dr. Anne, I see that your hand is raised, go ahead and speak.

Dr. Anne: Thank you. This is going back to the tether device, and one of the most common adverse events associated with this is the overcorrection of the instrumented curve and it is listed as 21%. However, further down in the materials, it mentions that the literature review indicates about 3%, 3% to 4%. So, is there--? I mean, it just seems-- I mean, that's five times higher. Is this specific just to peds, the higher adverse event rate, or is it just the general population for this particular device? And what are the measures being taken or could be taken to help minimize that?

Mr. O'Neill: Yeah, so I think the best answer that comes to mind for that good question is there are a lot of patient factors in the growth velocity or speed rate of growth, and the amount of curvature that progresses in these patients. Its-- Over time, you can have some prediction, but it puts mechanical forces and stress and strain on these devices in not readily predictable ways, and that can contribute to these tether breakages and associated adverse events. It's a continuing area of research and development.

Dr. Anne: I guess-- Just a quick follow up. Is this overcorrection at the initial implementation of the device or is this as the child--? Once it's been implemented--? Once it's been inserted already?

Mr. O'Neill: So, yeah, my understanding is this is after growth occurs and the tether does its job, and maybe too well, where the convex side of the curve corrects and then becomes concave. There's also a rotational element to these growth-guided technologies and as the skeletally mature patient grows. I forgot the other part of your question, but can you repeat that, or rephrase the--?

Dr. Anne: What I was asking-- Yeah, I'm sorry. What I was asking was is this limited just to the pediatric population or just the general population if it's done in adults also?

Mr. O'Neill: Yeah, so tethers in terms of regulatory status are limited to the indication stated in the Executive Summaries, and those are for skeletally immature patients with Adolescent Idiopathic Scoliosis.

Dr. Anne: Thank you.

Dr. Fischer: Ms. Oster, I see your hand up. Go ahead.

Ms. Oster: Thank you. I would like to go back to the Medtronic Activa question, and I have two points I'd like to make. The first one was 21% of the data was eliminated because they didn't know the age of the patient. That was 108 reports. We need-- Every report matters. I want to know on a go-forward basis what we are going to do to get age data so that we just don't eliminate it. And then my follow-up question to that will be: In the report on chart one, they showed how many MDRs there were, but they didn't show how many devices, and not seeing the correlation between the adverse events and the number of occurrences really is not giving us enough information to understand the frequency. So, on a go-forward basis, I would like to see chart one, which was on page six, include both pieces of data.

Ms. Clayborne: Hi, I apologize. I didn't provide my title and everything when I first spoke about the UDIs. I am a Health Scientist in the Division of Neuromodulation and Physical Medicine Devices in the Office of Neurological and Physical Medicine Devices.

As to your first question about the unknown age data in the Executive Summary, so for the MDRs, it is a passive surveillance system. We do receive over 1.4 million MDRs on an annual basis, and sometimes the information such as the patient's age and date of birth may not be reported, and in some instances they might not even know that information such as adverse events that are reported through social media, just for an example. The FDA does follow up primarily with manufacturers to obtain the missing information based on the seriousness of the event described in the report and the need to evaluate an issue for if there are trends or potential safety signals.

Those are prioritized for follow-up. Manufacturers also have work instructions and they have standard operating procedures that they follow for customer communication. That includes following up with questions such as those regarding any complaints or MDRs they receive. So, yeah, sometimes we do not have the information. I agree that it is important information, but since MDRs are imperfect, we make sure for the purposes of this PAC that we include the pediatric, known pediatric devices, the ones we use in pediatric patients, we ensure that we focus on that data because we don't want to assume any information.

Your second question about the chart one in the Executive Summary, the increase in the number of MDRs there was due to an additional 216 MDRs that we received following an FDA inspection of an operating unit within Medtronic that resulted in a change in how the firm handled their medical device report decision guidance for all of their operating units. So, that's why there is that spike there on that chart. As far as including the number of devices that were implanted during the timeframe, that can be included in the future. The devices that are implanted in that timeframe might not have an adverse event that matches within that one-year timeframe, so it might not-- It typically won't correlate, but yeah, that can be included in the future.

Ms. Oster: Thank you.

Ms. Clayborne: You're welcome.

Committee Discussion and Vote

Dr. Fischer: Any other questions from the PAC? Okay. If there's no more clarifying questions, we can move along to voting for the CDRH. Next slide, please. The Voting Question is being displayed on your screen. It states, "FDA recommends continuing review, ongoing post-market safety monitoring of each of the CDRH products under discussion." The question is, "Does the Pediatric Advisory Committee concur?" The options are "Yes, No, Abstain, or Recused." Are there any questions about the wording of this Voting Question? If so, raise your hand now. Dr. Baker, go ahead.

Dr. Baker: Yes, I am recused from one of the products. Do I recuse myself from voting on all of them or just-- How do I manage that?

Dr. Fischer: Shivana, I believe-- You can go ahead, but I believe the answer is just for the one product.

Ms. Srivastava: Yes, that is correct, doctor. Just for the one product. Yes.

Dr. Fischer: Thank you for confirming that. Any other questions about the wording of the question we're being asked to vote on? Okay.

I just need to remind any public observers that while the meeting is open for observation, public attendees will not participate except at the specific request of the panel. So, if there are any further clarifying questions on the voting, which I do not see any-- Members of the PAC, if you have any last questions here before we vote, go ahead and raise your name and state-- Raise your hand and state your name. I do not see anybody.

So, if there's no further discussion on the Voting Question, we can now begin the voting process. After the votes are collected, the vote will then be displayed on the screen and the Designated Federal Officer will read the vote from the screen into the record, then PAC members will then have the opportunity to summarize their votes into the record and state any reasoning that you have behind your vote. So, we will now commence the voting. Yeah, there you go.

This is Gwenyth Fischer. We are now ready to see the results. If they could go ahead and be displayed. You can go ahead and display the results and I will now turn the meeting over to the DFO. Next slide, please.

Ms. Srivastava: Thank you, Dr. Fischer. This is Shivana Srivastava. At this time, I will confirm that all Voting Members have received their voting ballots and all of the votes are in. Just to state, Dr. Holubkov has noted an error in his vote and will correct his vote once Dr. Fischer calls on him. For the Voting Question "Does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine, ongoing post-market safety monitoring for each of the CDRH products under discussion?" The results are: For LIPOSORBER, there are ten yeses, zero nos, zero abstains, and zero recusals. For Medtronic Activa Neurostimulator for Dystonia Treatment, there are eight yeses, one no, zero abstains and one recusal. For Minimally Invasive-- I'm sorry, for Minimally Invasive Deformity Correction, MID-C System, HDE, there are nine-- There are yes nines, one no, zero abstains, and zero recusals. For REFLECT Scoliosis Correction System, there are nine yeses, one no, zero abstain, and zero recusals. For the Tether-Vertebral Body Tethering System, there are nine yeses, one no, zero abstains and zero recusals. Thank you.

Dr. Fischer: Thank you. Now that the voting for CDRH has been completed, we will go down the meeting roster and have everyone who voted state their name, their vote, and if you want to, you can also state the reason why you voted as you did into the record. Again, if you see an error, please correct it for the record. We will start with Premchand Anne.

Dr. Anne: This is Dr. Anne. I voted "Yes" for all devices.

Dr. Fischer: Thank you. Susan Baker?

Dr. Baker: I voted "Yes" for all devices except Medtronic Activa, where I recused myself.

Dr. Fischer: Thank you. Douglas Diekema?

Dr. Diekema: I voted "Yes" for all products.

Dr. Fischer: Thank you. Charleta Guillory?

Dr. Guillory: Charleta Guillory. I voted "Yes" on all products.

Dr. Fischer: Thank you. Sarah Hoehn?

Dr. Hoehn: Sarah Hoehn. I voted "Yes" on all products. And I did appreciate the additional details about the spinal devices that were provided this morning.

Dr. Fischer: Thank you. Richard Holubkov?

Dr. Holubkov: Hi, Rich Holubkov. I voted "Yes" for all the devices based on my review and the discussion. However, due to potential conflict of interest issues, I would like to modify my vote for the Medtronic Neurostimulation device to recusal.

Dr. Fischer: Thank you. Liza-Marie Johnson. Liza-Marie?

Dr. Johnson: Thank you. Good morning. I voted "Yes" for all products as well. No recusals.

Dr. Fischer: Thank you. Gianna McMillan?

Dr. McMillan: Gigi McMillan. I voted "Yes" for all products.

Dr. Fischer: Thank you. Roberto Ortiz-Aguayo?

Dr. Ortiz-Aguayo: Roberto Ortiz-Aguayo. I voted "Yes" on all products.

Dr. Fischer: Thank you. Randi Oster?

Ms. Oster: Yes. I voted "Yes" for LIPOSORBER and "No" for the other four products. The reasons are as follows. For the Medtronic Activa on a go-forward basis, missing data due to age or-- Is just not enough for us to just continue with the current process. I would like the FDA to really reinforce something as simple as an age metric as going forward to improve the data. For the Minimally Invasive Deformity Correction, MID-C System, there were reoperations at 18%. There's a learning curve there, and I would like, going forward, that there's more information on how the learning curve affects results. For the REFLECT, there was information about overrepresentation and that the data that we were given they felt that it was double counted. Going forward, I believe you need to streamline that and I would like the FDA to look at how we could have the data be more reflective of that double counting. And the third one, or the last one, tether, there's a need for additional reporting for up to three years postoperatively, and I'd like the process to include that for ongoing safety surveillance. Thank you.

Dr. Fischer: All right. Thank you, everyone, for your thoughtful votes and comments. That will conclude the CDRH vote, so we can go to the next slide. Thank you.

Listing of products evaluated in the pediatric-focused post-market safety reviews completed by the Center for Biologics Evaluation and Research (CBER)

Dr. Fischer: We will now transition to the discussion about pediatric-focused post-market safety reviews completed by the Center for Biologics Evaluation and Research, CBER. This will be represented by Dr. Craig Zinderman. Next slide, please.

Dr. Zinderman: Okay, thank you Dr. Fischer. So, I'm Craig Zinderman, Associate Director for Medical Policy in the Center for Biologics Evaluation and Research, Office of Biostatistics and

Pharmacovigilance. We have four products for the advisory Committee today. Those products are Dengvaxia, Epicel, Fluzone Quadrivalent, and Gardasil 9. I'll turn the meeting back to Dr. Fischer.

Clarifying Questions

Dr. Fischer: Thank you. We can now go ahead and proceed with clarifying questions from the PAC. I'll just remind everyone to use the "Raise hand" button so that I know to call on you. When called upon, if you could please state your name for the record before asking your question and we will, again, just ask one question at a time and I will circle back to you as time allows if you have further questions. We'll go ahead and start with individuals who submitted questions to the Agency in advance of the meeting. And again, when I call your name, please read your question into the record. And again, if you submitted multiple questions, I will circle back with you as we have time. So, we can go ahead and start with Randi Oster.

Ms. Oster: Yes, thank you. This is Randi Oster, the Consumer Representative. My question has to do with D-E-N-G-V-A-X-I-A. And my specific question has to do with the fact that there were among 119 foreign deaths reports with unknown age, and that was the reason for excluding these reports. As I talked about earlier, each data point is significant and it doesn't matter if someone's six or seven, it might matter if they're six or 60, but to say that we're excluding the data because we do not know their age, I would like on a go-forward basis, a process to capture that age.

Dr. Zinderman: Yeah, thanks for the question. First, I just want to address the data wasn't excluded. We don't exclude cases from our reviews. It was in the reviews and in the tables and data provided to you in the Memorandum. There were 120 foreign death reports that appeared to have missing age data in the VAERS results that were provided in the Memorandum. Individuals might omit the age from the age fields in a VAERS report for a number of reasons. They might not know the exact age of the patient. They might leave it blank. It might just be easier for them to write a description of what happened and cover the age in the description than fill in all the fields in the report. There's any number of reasons. But in that

description, and then what we call the narrative, where they write about the report, they might have more information about the age of the patient. They might mention that it's a child or they might give the specific age later on in the report. Based on our review of the case narratives, we were able-- We do have additional information on these patients, and I'll come back to why we didn't present this information in the review. There was one report with a vaccination date after U.S. approval, so this is a case that occurred, or at least that was received after the time that the product was approved in the U.S. So, these are all foreign reports that we're talking about. This report that was associated with use in the Philippines and doesn't involve-- Or happened preceding U.S. approval. This report had unknown age, but we determined that it involves a pediatric patient, and this report is described in the Memorandum in more detail. Among the other 119 reports with unknown age, 86 were determined to involve pediatric individuals, and we've given that number, 86, in the Memo.

I have some more details that I can provide for you today. 48 of the report's narratives indicate a specific age ranging from 9 to 16 years. 35 reports indicate that it was a child. We don't know the specific age in those 35 reports, but we do know-- That's the reason we know they're pediatric. Two reports mentioned the age between 10 to 12 years, and one report says it was a fifth grader. That's a total of 86 reports in pediatrics. Five cases listed the age as an adult. These were 20 to 39 years old. And that leaves 28 reports with the age still unknown after describing or after reviewing the narrative. So, a total of 86 of the 119 reports appear to be for pediatric individuals, 5 were for adults, and 28 continue to be for unknown age. We want to note that this information is-- On the specific age of these 119 patients would not impact the findings or provide additional insights into safety in this review, in our opinion, because all of these cases were associated with the risk of dengue, or severe dengue, or subsequent dengue after vaccination if you vaccinate without knowing the patient's prior status with regard to prior dengue infection, if that information is unknown at the time of vaccination. So, that's a restriction in the indication for the U.S. When it came time for U.S. approval, all of these cases had already happened, and

so that's a restriction in the U.S. indication. You should only vaccinate people for whom your history of dengue infection is known.

Ms. Oster: Thank you.

Dr. Fischer: Thank you. Randi, do you have any other questions regarding Dengvaxia?

Ms. Oster: No, but I'll go on when you get to the other--

Dr. Fischer: Sure. Does anybody else have questions regarding that particular vaccine? Just so we can keep organized here. Okay. Dr. Hoehn, I believe you had some questions. Go ahead.

Dr. Hoehn: Thank you. Sarah Hoehn. I had questions about the death reports for the Gardasil vaccine on page 10 and 11. The three-- I know that there were six reports, but the 12-year-old, the 10-year-old and the 14-year-old all seemed a little bit similar in the overall neuroinflammatory category. So, I wondered if the FDA could comment on whether or not they thought there was any link or any concerns given the similarity of those. I feel like we see a lot of different death reports from all different reasons, but the fact that those three seemed similar, I wanted additional-- What the thought process was behind those in terms of any linkage.

Dr. Zinderman: Yeah, there were a couple of death reports related to ADEM, ADEM and other neuroinflammatory conditions during the period of this review. We do not believe that ADEM reports for Gardasil represent an outlier at this time. We want to note that ADEM is labeled in section 6.2 for Gardasil because there have been reports over time. It was labeled prior to the PAC review period. It's been labeled for some time. So, reports of ADEM after Gardasil is a known occurrence. ADEM is a demyelinating disease of the brain and spinal cord. It's commonly triggered by viral or bacterial infections, although it has been described in case reports after various vaccinations. It generally occurs four to six weeks after the initial infection as an autoimmune process. So, since ADEM occurs in the

background population and it can be caused by infections not infrequently encountered, and the rate in the general population is estimated to be 1 in 125,000 to 250,000 per year. It's most common in children less than 10 years of age who tend to have a higher frequency of infections throughout the year compared to adults.

So, as described in our review, there were a few reports, a few unfortunate death cases associated with ADEM or an ADEM subtype. However, in our view, the number of these cases is fairly small, particularly in relation to the estimated number of marketed Gardasil 9 vaccine doses distributed worldwide during this time period, which is over 200 million. There have been also-- We should mention a couple of controlled observational studies comparing vaccinated periods of time or vaccinated individuals to unvaccinated cohorts. And these studies looked at autoimmune conditions and did not find an elevated rate compared to the unvaccinated groups. We can provide some information on those later. So, our assessment is that the ADEM has not been reported in numbers that suggest that it occurs at an outlier rate following Gardasil as compared to the background population or to other vaccines.

Dr. Hoehn: Thank you. No, that makes sense in terms of numerator and denominator, so thank you for that.

Dr. Fischer: Just to keep on theme here, any other questions regarding Gardasil, specifically?

Ms. Oster: Yes, this is Randi Oster. I have Gardasil questions.

Dr. Fischer: Go ahead, Randi.

Ms. Oster: Thank you. So, with the Gardasil, I wanted to know if the literature review included any lawsuits. There were over 200 lawsuits and I don't believe that was in the literature review. I'd like to understand how we can incorporate some of that information as we're going forward. And also, what I've- - In my last six years as being the Consumer Representative, I have seen how literature reviews could be

expanded to social media pages where patients are starting to find an opportunity to share their information. They might not be putting it into MedWatch, but they have been, and we've actually done some black box warnings where patients came together on Facebook, and so I'd like you to comment on expanding the literature review to include lawsuits as well as social media.

Dr. Zinderman: Thanks for the comment. The literature section includes publications in peer reviewed scientific literature. We don't search specifically for or incorporate lawsuits into the reviews. That said, manufacturers are required to report to VAERS cases that have been reported to them as part of a lawsuit. These cases are considered the same as spontaneous reports that might be submitted to them by a healthcare provider or a consumer. These reports are continuously evaluated on a routine basis as we do with all VAERS reports, all reports submitted to VAERS. We should note that as lawsuits often contain confidential information, reports from lawsuits often are limited in the relevant-- Amount of relevant information and clinical details that they have, and this can be complicating or precluding in terms of assessing causality.

With respect to social media, manufacturers are also required to report, and do report, adverse events that they become aware of via social media, and they also attempt to contact sponsors-- Contact social media reporters to find additional information. Although this is often fairly low yield, as you can imagine, and it's difficult to get, again, relevant clinical details from these cases. We do, of course, welcome information from the general public about adverse events experienced after receipt of vaccines, and there's information on how to report to VAERS available on YouTube and Facebook.

Ms. Oster: Thank you.

Dr. Fischer: Thank you. I don't see any other hands up. Are there any other questions regarding these two products or any of the other products that the CBER team has presented today? Randi, go ahead.

Randi, you can go ahead and speak if you'd like. [Silence.] Randi, the floor is yours if you'd like to say anything else.

Ms. Oster: Yes. Oh, I'm sorry. I just want to get-- Just give me one second. The next one was Flurozine [sic.] right? And-- One second.

Dr. Fischer: Fluzone?

Ms. Oster: The Fluzone.

Dr. Fischer: Fluzone Quadrivalent.

Ms. Oster: I have to do it this way. Give me one second. I want to get to-- I apologize, my-- All right. If someone else has a question, just give me-- Oh, here it is. I found it. Okay. The Fluzone. Oh, my question has to do with how do we look at vaccines and see if they're reacting with each other? What is the process change that the FDA can make so that we capture that data?

Dr. Zinderman: Yeah, so we certainly agree that safety following co-administration of vaccines is extremely important to assess and monitor as we do with concomitant administrations of any products that are frequently administered together. For many products, we should note that co-administration is evaluated as part of the clinical and preclinical studies as part of the clinical development program prior to approval, so there's normally some studies of multiple products administered together to assess safety and effectiveness when all those products are given.

We also want to note that the ACIP, the CDC's Advisory Committee for Immunization Practices, is the entity that recommends the childhood vaccination schedule and they consider all available data and other evidence, both pre-market and post-market, as part of their work group's evaluation of which vaccines should be given together and the safety of those combinations. It's beyond what we can really say specifically about Fluzone, but there have been a number of-- A robust number of studies on co-

administration, and generally these studies find a minor increase in risk of certain reactogenic types of adverse events like fever, but no significant imbalances in safety compared with administering each of the vaccines alone.

To all of that said, as you suggest, as part of our usual post-market monitoring, we do evaluate and consider all the exposures in any individual case as well as comorbidities and other host-related factors in that case. Any adverse events that we consider for needing further evaluation as a possible safety issue, a safety concern that we're starting to work up to see if that concern is maybe causally associated with a vaccine, we're of course going to look at. You know, what were the cases in that vaccine administered alone? What were the cases in that vaccine administered with other vaccines? What other vaccines, what are those combinations? As well as looking at other factors like seriousness, the frequency of the reports for each category, and other concomitant exposures as well as the patient's age ranges, comorbidities, sex, and other factors. And last, there were a couple of cases in the Fluzone review that described multiple vaccines administered that does make definitive assessments of causality difficult and complicated, but that's how vaccines are administered. We should note that the presence of these cases doesn't necessarily mean there's a safety signal associated with administering multiple vaccines as compared to administering the vaccines alone or as compared to the rate of those same conditions in the background population, in an unvaccinated population. Thanks for the question.

Dr. Fischer: Thank you. Ms. Oster, I don't see any other hands up, so if you have further questions, you have the floor.

Ms. Oster: Yep, thank you. I just have-- The last is on the Epicel, and I want to understand the process for capturing additional time-to-graft data, and then also understanding a little bit about what training and processes worked in the past and if we're going to continue monitoring how we're going to use additional effort to get better data going forward.

Dr. Zinderman: So, with respect to the time to graft-- Sorry, time from graft to event. So, this is the number of days, for example, between the time a burn patient, a burn injury patient, receives an Epicel graft to the time that they have the adverse event that's reported in the review. Many of these cases, unfortunately, were fatalities, so oftentimes the time from graft implant to the time of death. There were 10 of these cases reported in our review, and for several of them we did not have detailed information on the time from graft to death. We do have additional information that we were able to locate on four of those cases subsequent to the review. So, the four cases that are presented in table three in the review, the time to event from grafting was-- The event occurred on the day of grafting in one case, 37 days in two cases, and then 40 days after grafting in the fourth case. We want to just remind folks that these events are collected as spontaneous reports either from clinicians involved in the case, sometimes family members, the hospitals where the events occur, and other healthcare providers and consumers, and some information may be missing despite due diligence on the part of the manufacturer to contact these individuals and obtain additional information. We can't compel them to provide it or they might just not have it.

Ms. Oster: And that's what I just want to focus on, for going forward, right? That's what the purpose of this vote is for. You talked about that it could be spontaneous information; we might get it from the family member. What can we do as the FDA to make sure that we get the data that we need and that we change the process going forward so that in our next review we do not have this type of data?

Dr. Zinderman: Yeah, we can be sure to contact the manufacturer and ask for additional follow-up at the times that we receive the case. As I think our CDRH colleagues noted, there are over a million, I think several million reports received each year for devices. That's not always possible, but for certain key characteristics, we can try to do that. Like I said, that's not going to produce data in every single instance, but that's one step that can be taken.

Ms. Oster: Thank you.

Dr. Fischer: Thank you. Dr. Hoehn, did you have another question?

Dr. Hoehn: Yeah, this is Sarah Hoehn. I just had a question about the Epicel in terms of the number of failure rates coming out of the pack, like when it was first coming out, the defective grafts, it was on page 10. Is that number of defective grafts similar to other grafts or other types of things that are done for kids with severe burns? It just seemed like a high rate of defective grafts. So, that was my question.

Dr. Zinderman: So, we'll talk a little bit about the manufacturing issues that were described in the review. So, we want to emphasize first that these are grafts that were not implanted into patients, so there's no associated adverse event. We consider these product quality issues, problems with the graft at the time that it arrives at the hospital for use. As the label states, Epicel consists of sheets of proliferative autologous keratinocytes ranging from two to eight cell layers thick. Each graft of Epicel is attached to the petrolatum gauze backing with titanium surgical clips. Given the complexities of manufacturing, some grafts can become detached from this backing, from the gauze scaffold, but patients are not grafted with the product when this happens. The surgeon can identify that this has happened. It's not a graft that they would necessarily implant. They can identify that pretty easily just visually examining the graft, so they're usually discarded, and so there's no safety signals that we would expect to be associated with the manufacturing issue. It's also labeled that the graft detachment can occur. It's part of the Epicel instructions for use and labeling.

Regarding other grafting options in burn injuries, I don't have a lot of information about that. Autologous split-thickness grafts, of course, is the standard of care, although in patients with greater than 30% body surface area burns, there may be limited donor sites. Many of these Epicel patients have far greater percent burn areas than 30%. As far as the corrective actions that were in place, the manufacturer reported that the total number of grafts impacted by this issue was reduced between 2023 and 2024 and FDA will continue to monitor their progress on this issue and work with them to make sure that it continues to improve. A large number of grafts are generally ordered and grafted per person. You'll see

earlier in the review that there's an average of 90 grafts per person, so the proportion of grafts that are impacted by the quality issue is usually fairly small, so there's still a large number of grafts that can be used for each individual case. And so that, on top of the improvement, the decrease in the percentage of grafts year over year, we do assess the impact of this problem to be fairly small.

Dr. Hoehn: Thank you very much. I don't have any follow-up questions.

Dr. Fischer: Thank you. Any other questions? I don't see any other hands up. Please, put your hand up if you have any follow-up questions for CBER here. Okay. I don't see anything, so I think we can go ahead and proceed with the voting for CBER . Next slide, please.

Committee Discussion and Vote

Dr. Fischer: We will go to the Voting Question. If you could display that on the screen. It states, "FDA recommends continuing routine, ongoing post-market safety monitoring for each of the CBER products that we just discussed." The question is, "Does the Pediatric Advisory Committee concur with this plan?" The options are "Yes, No, Abstain or Recused." Are there any questions specifically about the wording of this question? Please, raise your hand if you have a question about the wording. Okay, I don't see any questions.

I just want to remind our public observers that while the meeting is open for public observation, public attendees may not participate except at the request of the panel. If there are no further questions, we can now begin the voting process. After the votes are collected, the votes will then be displayed on the screen and the Designated Federal Officer will read the vote from the screen into the record. PAC members will then have the opportunity to summarize their votes, just like the last time, into the record and state any reasoning behind your vote. The voting will commence and you should see a pop up as soon as we set that up. Give the team here a minute to set up the voting.

Dr. Fischer: Okay. Welcome back, everyone. It's Gwenyth Fischer. We are ready to see the results, if they could be displayed. I will turn the meeting over now to our DFO.

Ms. Srivastava: Thank you, Dr. Fischer. This is Shivana Srivastava. For the Voting Question "Does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine, ongoing post-market safety monitoring for each of the CBER products under discussion?" The results are: for Dengvaxia, there are 10 yeses, zero nos, zero abstains, and zero recusals. For Epicel, there are 10 yeses, zero nos, zero abstains, and zero recusals. For Fluzone Quadrivalent, there are nine yeses, one no, zero abstains and zero recusals. For Gardasil 9, there are eight yeses, one no, zero abstains, and one recusal. Thank you.

Dr. Fischer: Thank you. Now that the vote for CBER has been completed, we will go down the meeting roster and have everyone who voted state their name, their vote, and if you'd like to, you can state the reason why you voted as you did into the record. If you see an error in the vote that was just posted, please correct it for the record. We will start with Premchand Anne, please.

Dr. Anne: This is Dr. Anne. I voted "Yes" for all four agents.

Dr. Fischer: Thank you. Susan Baker?

Dr. Baker: This is Susan Baker. I voted "Yes" for all agents except Gardasil, for which I recused myself.

Dr. Fischer: Thank you. Douglas Diekema?

Dr. Diekema: Doug Diekema. I voted "Yes" for all products.

Dr. Fischer: Thank you. Charleta Guillory?

Dr. Guillory: Charleta Guillory. I voted "Yes" for all four products.

Dr. Fischer: Thank you. Sarah Hoehn.

Dr. Hoehn: Sarah Hoehn. I voted “Yes” for all four products and partly because the rates of what we were seeing are not any higher than occur in the general population. And all my questions were addressed. Thank you.

Dr. Fischer: Thank you. Richard Holubkov? Dr. Holubkov, we can't hear you.

Dr. Holubkov: Oh, hi. This is Rich Holubkov. I voted “Yes” for all four products.

Dr. Fischer: Thank you. Liza-Marie Johnson?

Dr. Johnson: Yes. Liza Johnson. I voted “Yes” for all products. I had no concerns after reviewing the materials and hearing the discussion.

Dr. Fischer: Thank you. Gianna McMillan?

Dr. McMillan: Gigi McMillan. I voted “Yes” for all products.

Dr. Fischer: Okay. Thank you. Roberto Ortiz-Aguayo?

Dr. Ortiz-Aguayo: Sorry, I couldn’t see my button here. Roberto Ortiz-Aguayo. I voted “Yes” for all products.

Dr. Fischer: Thank you. Randi Oster?

Ms. Oster: Yes. I voted “Yes” for the first two products and-- Because my questions were answered and I'd like to say thank you for that. And then for Fluzone and Gardasil, I voted “No.” I would like the ongoing studies for the FDA, for Fluzone, to really look at multiple vaccines and what they can do differently going forward and to improve that process. And for Gardasil, I think the expansion of getting

information through MedWatch and a process to capture that as well as looking at other literature reviews and information to really help with the data on that particular drug. And that is why I voted "No."

Dr. Fischer: Okay. Thank you for everyone's thoughtful questions and commentary regarding the CBER presentation and voting. We can go to the next slide now. Okay. It is lunchtime. Just a reminder, panel members, please remember no communication of the meeting topics throughout your break. And probably the easiest thing to do is to just continue your Zoom on here and just shut down your audio and video. We will resume at 1:00 p.m. eastern time sharp. Is it 1:00 or 1:30, Shivana?

Dr. Hoehn: The agenda only listed 30 minutes.

Dr. Fischer: Okay.

Ms. Srivastava: It'll be 1:30 when we resume the meeting.

Dr. Fischer: Okay. Thank you. So, clarification, we will resume at 1:30. I apologize. So, at 1:30 eastern time, please be back here and we will resume.

Listing of products evaluated in the pediatric-focused post-market safety reviews completed by the Center for Drug Evaluation and Research (CDER)

Dr. Fischer: Welcome back, everyone, from lunch. We are now going to proceed with the PAC meeting, and we'll transition to the discussion now about pediatric-focused post-market safety reviews completed by the Center for Drug Evaluation and Research represented by Dr. Ivone Kim. Dr. Kim, go ahead. Thank you.

Dr. Kim: Hello. It's nice seeing everyone. All right. Let me make sure the screen is up. So, thank you Dr. Fischer. For the record, my name is Dr. Ivone Kim and I serve as a Senior Medical Officer in the Office of Surveillance and Epidemiology in CDER's FDA. So, I will now read a list of CDER regulated products that are under discussion at today's meeting. Please note that I'll be stating the trade names only,

but as a reminder to the audience, both trade and generic names will be listed in the following slides. Please note also that in some instances more than one product was included in the same review, and products that were listed-- Reviewed together are listed together in the slide and will be voted on together at the conclusion of the Committee's discussion.

So, I'll now begin reading the products. AUVI-Q Auto-Injector; Diovan; Entresto; Eraxis; Eucrisa; Exjade, Jadenu, Jadenu Sprinkle; Fiasp; Jakafi, Opzelura; Latuda; Liletta. Next slide, please. Mycamine; Nityr; Potassium Phosphates; Repatha; Rozlytrek; Stelara; Sutent; Tasigna; Topicort; Triumeq, Triumeq PD; and Xyrem. Thank you. I'll now transition the meeting back to Dr. Fischer, PAC Chairperson.

Clarifying Questions

Dr. Fischer: Thank you, Dr. Kim. We will now proceed with clarifying questions regarding the list presented here by Dr. Kim. I'll remind you to just "Raise your hand" button if you'd like to be called on. When you are called on, please go ahead and state your name for the record before asking your question, and we will try to do one question at a time as we previously have today. We'll begin with individuals who've submitted questions to the Agency already in advance of this meeting. I will try to group these since we have a number of products here, I'll try to group the questions as much as possible around the product. So, if someone is speaking on a product and you also have a question, please raise your hand and we'll try our best to group those for our FDA folks who are answering the questions. Randi, I believe that you had submitted some questions and I see your hand raised, so please, go ahead and speak.

Ms. Oster: Thank you. So, the first question has to do with epinephrine, and what I would like to understand is how you extrapolate the data from the adult population for adverse events that might lead to pediatric conditions. Is there a correlation between the 13 adult deaths and pediatric cases? And did the review include this correlation? And then also just if you can comment on any reports that came in through MedWatch, and so on a go-forward basis, my hope is that we start to increase awareness for

MedWatch. And I just want to finish my last thought here, is: How do we increase awareness for possible device malfunctions including inaccurate dosage delivery and failed to deliver the intended dose? Thank you.

Dr. Kim: Thank you for your question. I'll answer the first part about extrapolation first. So, because the focus of these post-marketing pharmacovigilance reviews for the PAC is on new safety signals in pediatric patients, we do not include adult data in these documents, but as part of routine pharmacovigilance activities that we do outside of PAC, we review adverse event reports for patients of all ages. So, that includes adult and pediatric reports. And we also review actually other data streams too for adults and peds as well. Although we don't include that data in the PAC review, we use the knowledge that we gather in the pharmacovigilance of these patients that-- To inform our review of each case that we do for the PAC. So, I'll address that.

As far as MedWatch goes, all the reviews, all the reports that we include in the review actually derive from MedWatch FAERS, so they're all MedWatch. So, you know, we are always trying to increase visibility of and awareness for reporting. I know from a systems level, FDA has multiple programs and we do outreach through media to increase awareness and education about reporting. We also put out safety communications as well as publication, once to promote the pharmacovigilance program findings, but also to encourage people to contribute to drug safety reporting.

I think your last question was about device malfunction. So, it's a great question. So, when CDER conducts post-marketing pharmacovigilance review, so safety surveillance for all products, that includes adverse event reactions, potentially. And then we also look at medication errors and device malfunction issues. So, some of the surveillance, this is part of the routine pharmacovigilance we do, that's conducted by specialized offices. I think for this product specific was the only one that included reports for device-related issues. So, I'll note that there were six cases that identified like device issues, and the receipt of those cases actually corresponded in time with a voluntary recall of the product back in

2015. And that was due to potential product quality concerns. So, FDA actually reviewed that safety issue at the time and the applicant actually did a root-cause analysis and they were able to submit a supplemental application that supported manufacturing changes that then supported the-- Like more better device reliability. And the manufacturer of the product they were actually able to resume that in 2017. At the time we finished the AUVI-Q review for the PAC, FDA had not received any other serious pediatric FAERS reports related to device quality issues since 2016. So, we were pretty reassured in terms of that.

Dr. Fischer: To the PAC group, are there any other questions around AUVI-Q specifically? I don't see any other hands raised. Ms. Oster, I believe you have a couple other questions. You can go ahead.

Ms. Oster: Sure. So, my second question is on the next drug, which is valsartan. And what I would like to know is what is the safety plan to review outcomes for adults to determine the commonality with pediatric patients? In this case, there were over 2,000 adult deaths and there were 23 pediatric deaths, and I know we do endpoint when we're approving the drug if it's going to help them. And I just want to take the time with such a high death rate for the adults to discuss what we can do here, going forward, for pediatric patients.

Dr. Kim: As I stated, because the focus of these reviews is on pediatric safety, we don't include adult data. I think maybe part of the question may relate to extrapolation of adult data. I guess-- Before I go into that, I just wanted to address some deaths. Not all deaths will be related to the drugs. It can be related to the indication for the drug use and other comorbid condition. That said, when it comes to extrapolation, it's a little bit beyond the scope of this meeting. There are some data considerations that would not favor blanket extrapolation of adult patient data to pediatrics. There's, first of all, the issue of the limitation of the spontaneous reporting system, what we can do with that data, you know, preclude some calculation of incidence rates and extrapolation from that. There's also consideration for pediatric physiology, pediatric pharmacodynamics and diseases that are specific to pediatrics. So, we can't just compare. It's not necessarily apples to apples comparing adults and peds.

Ms. Oster: Thank you.

Dr. Fischer: Any other questions from the PAC about Diovan, also called valsartan? Okay, Randi, you can continue if you'd like.

Ms. Oster: Yes, thank you. So, my next drug is Entresto. And 47% of the reports were eliminated due to comorbidities or other reasons. And that's a lot of reports, that if there is some correlation that people are taking a medication and there are patterns here, there's an opportunity for the FDA on an ongoing surveillance to start to learn about this so there could be some warnings. And so, I'd like a comment about that and I'd also like a comment about unaccessable data. In this case there were four, including a death, and the report couldn't be assessed because there was insufficient information. Each report is a key piece of data. And so, for future, what is the FDA going to do to start to improve our ability to use the reports that come in, instead of just eliminating them and saying we didn't get the information we needed?

Dr. Kim: Thanks for your question again. So, I'll go back to your first question, right? I'll reiterate what our colleagues in CBER said. So, we don't dismiss or exclude any report. Every single report that we identify in these reviews are actually really thoroughly analyzed and reviewed. We do perform case-level reviews on every single one. So, across the 21 documents that we present in this PAC cycle, there are a little over 2,200 reports and every single one of them was thoroughly assessed. And it's actually because of these assessments that we're able to determine that there was no new safety signal in peds with this specific drug in question. Sometimes the cases that we review make compelling cases for causality with another drug or another condition. Some adverse events can occur from other exposures or a consequence of an underlying disease. For example, we may see that there is an adverse event of bowel resection, but it's closely clinically tied with a diagnosis of necrotizing enterocolitis. So, you have to make a clinical judgment call, right? But, we focus the reviews so they're not included for further discussion in the reviews, but they are not excluded from review, if that makes sense. So, if they are-- Like, if the adverse

events are closely tied and clearly secondary to a concomitant medication, a comorbidity, or disease progression, then we don't further discuss it because it's not tied to the drug in question.

So, for your second question, I think there's actually maybe two parts to it and I'll try to talk about both. I think part of it is the issue of missing data from reports. So, we agree missing data can be an issue. FAERS data derives from spontaneous adverse event reporting and just by nature it's going to have some variability in the level of information that we get. That's partly by design because to remove some barriers for reporting, we make it pretty easy for people to turn in reports to FDA. There's only four criteria for submitting an adverse event report to FAERS. You just need a reporter, you need a patient, you need a drug, and you need an adverse event. Some reports, therefore, can miss some information that we would like to have. We try to mitigate the missingness of data by, you know when possible, reviewing source data, sending information requests to drug companies and following up with reporters. But again, as I said before in previous presentations, it's hard. Despite these outreach efforts, we don't always get the data we need. Sometimes the reporters don't have it, sometimes they can't be compelled to produce it, right?

But the second part of the question was on unassessable reports, and that's kind of related to the reports that were not further discussed because they're concomitant medications for underlying disease-related reports. So again, we review all the cases that we identify, right? So, the goal is to identify new safety issues and part of how we determine whether or not there's a safety issue is we do a causality assessment. So, the term “unassessable” does not equate “unusable,” and it doesn't necessarily say that there's no data, it’s just that it didn't meet the threshold to reasonably determine that the drug we're looking at caused the adverse event. So overall, I think across the 21 reviews that we presented to PAC this cycle, about 14% of all cases were deemed to be unassessable, right? And again, they're reviewed, they're not unusable. Remember that these cases remain in our FAERS database and they may be useful for analysis in other post-marketing pharmacovigilance reviews that we perform and they may support like a causal association with another drug or another scenario.

Ms. Oster: So-- Just to summarize, so you don't think there's anything that the FDA can do to approve this rate on a go-forward? Are you satisfied with the rate as it is now? In other words, we're not trying to approve it, we're just saying-- Because the question that we're going to be answering is "Yes, continue as we're doing" or "No, look for ways to improve the quality of the data," basically. And so that's what my question is that there's no additional methodology or processes that the FDA is looking at putting in to improve the rate of missing data, or unassessable, or concomitants.

Dr. Kim: So again, because unassessable refers to causality assessment, it depends on the question you're asking, right? So, the same report or case can be unassessable for one drug or one question but may be informative for causality for another drug. So, unassessable and unusable are different things, and that depends on the assessment. For missingness of data, I mean, it is a concern with any spontaneous adverse reporting. So, we have continuous efforts, from a program level to continue educational outreach and media and to fill in the missingness of data. But missingness is also relative, it depends on the assessment that we're doing. For the purposes of the pediatric post-marketing reviews that we perform for PAC, though, unassessable rates, just depends on whether or not we have enough information to reach the threshold, again, to reasonably determine that the drug that we're looking at caused the event.

Ms. Oster: Thank you.

Dr. Fischer: Thank you, Dr. Kim. Questions from PAC? I see Dr. McMillan, go ahead.

Dr. McMillan: Yeah, I just wanted to state for the record that Randi, I agree with every comment that you've been making. I think we're all troubled by missing data and missing ages, for example, in some of the subjects. And we are voting, in my opinion, on whether we want continued review on all of these pediatric agents. We're not voting on what kinds of changes could be implemented into the data collection system. And frankly, I think that would be a great topic for another meeting because there's so much data that's missing globally that perhaps that could be a specific topic for this group. Is there anything that we

could reasonably request or design that would improve the data collection process? But I do feel like our hands are tied. The process is what it is, and there's so many individual circumstances that we pretty-- In my opinion, we have to vote "Yes, please continue getting information" because the alternative is "No, don't get any more information, don't continue getting information." And the question about "Can we change or improve the process?" is a different matter altogether.

Dr. Fischer: Thank you, Dr. McMillan. When I summarize at the end of the meeting, I'll make sure to make a note of that as well as what Ms. Oster-- Some of her recommendations as well so that it's in the record. Other questions or comments specifically about the 21 products listed, or any follow up from this conversation so far? Ms. Oster, go ahead.

Ms. Oster: Yes, thank you. And again, I appreciate the patience that you're having. I am the Consumer Representative and I believe it's important that the voice of the people are shared and that is why I've taken the time to go through each of these drugs with each of these questions. The next one is on Eucrisa, and my question there is when it's a labeled adverse event, and I don't want to use the wrong word, it's not eliminated, I understand you look at it, but it doesn't count for the review that we're doing now. And from the point of view in this drug, 26% of the data that came in was considered already a labeled event from a consumer point of view just because they were told it was a problem. If we're getting that kind of level of response, that "This adverse event affected me," what is the acceptable level where then the FDA might say, "Wait, even though we put it on the label, at what point do we need to look at our labeling?"

Dr. Kim: That's a great question. So unfortunately, I'll point to one of the limitations of the database again. Because it's a spontaneous report, we can't capture rates necessarily. There's no denominator. So as far as the FAERS reports go, there's no rate that we can pinpoint to say, "Oh, this is a problem," right? Now, labeled events, it's important to review cases that describe events that are labeled and why, because we're still trying to find new safety concerns. As far as labeled or known adverse events

go, we're looking for different features that might say, “Hey, there's reason to be concerned about a new safety issue here.” And features include potential increase in severity of already known adverse events, or it can be increased specificity. So, for example, maybe hypersensitivity is already labeled, but we are seeing cases of anaphylaxis, so we're not necessarily looking at rates, but we're looking at different features of these events and that might be a trigger for us to do a further evaluation and do some regulatory action.

Ms. Oster: Thank you.

Dr. Fischer: Randi, go ahead and continue.

Ms. Oster: So, I just want to just comment then for Exjade, we're going to start to see the same pattern. And this is important, I don't have to ask the question for each drug, but I do want to point out the pattern. So Exjade, 57% of the reports were eliminated for adverse events. So, we're starting to see people are-- That's just a huge number. And that included some deaths, and sometimes these are also boxed warnings. I also want to comment that in this particular case with Exjade, 20% of the reports were unassessable. So, you start to look at the number of reports coming in and they're just not usable. And that's my concern is that-- and I'm going to take the time here. The reports that are coming in are through the FAERS database, and in our training last month, we were trained that the FAERS database is submitted from the manufacturers, and the MedWatch databases are typically submitted from the consumers. And 95% of the reports that are coming in are coming in through FAERS, which is the manufacturers. So, it's already first the consumer, the patient, to go to the manufacturer, we've already eliminated so much. And I just would like you to comment a little bit about what are we doing here with the reports that we do have. I know you've said it, but it's very hard to just say-- I'm not saying we shouldn't continue monitoring, but just to continue on this same process without acknowledging, I think would be a misstep.

Dr. Kim: Sure. So, thanks again for the question and I appreciate you trying to dissect a nuance. So again, the same, I'll repeat my answer regarding the labelled adverse event, right? We are not excluding them and they're not unusable, they are usable reports because they're informing us that at least for that case, there's no indication that there's a concern, right? Potentially there's no indication because there's no clinical features that's saying that it is a new safety issue. Now, as regards to what-- Something that's labeled that it's in a different section of the labeling, whether it's a box warning or a warning and precautions, we address each labeled event the same way. We have to apply the same scientific rigor to see like, "Hey, are there new features of this that warrant new, further evaluation and maybe elevation of FDA communications?" So, because we don't include the report for further discussion doesn't mean that we are not evaluating it. Because the assumption there is that there's always going to be something bad, but that's the evaluation, "Is there something bad going on or not?"

Now, as regards the FAERS database, I do want to make a little correction. So, FAERS is our database of all post-marketing reports. MedWatch is the program that we have that feeds into FAERS, right? And we receive adverse event reports. Adverse event reports can come from the patients or consumers themselves. So, they call FDA through the MedWatch forms, or contact us through the MedWatch forms, and they submit a report. Companies-- Patients can also contribute reports and get in touch directly with the drug manufacturers. And those manufacturers are compelled by law to send over all those reports to FDA. So, that quote of about 5% of consumer reports, it's not consumer reports, it's direct reports. We're saying that the patients and consumers are directly reporting to FDA, the MedWatch, which then ends up in their FAERS database. And then 95% is the people that are reporting to the companies who then are sending things through MedWatch and it ends up in the FAERS database. If you actually look at all the FAERS data and you look at where the reports are coming from, about 50% actually comes from consumers, and the other 50% comes from healthcare practitioners. So, I think the consumer voice is being heard, in fact, they contribute a lot of data, so I wanted to clarify that.

Ms. Oster: And that is new information that was not shared during our training. So, thank you.

Dr. Fischer: Ms. Oster, any other comments specifically on the products at hand here?

Ms. Oster: So, I don't know if anyone else has any other questions. I just want to-- Because I will--

Dr. Fischer: You can keep going.

Ms. Oster: Okay. I'm going to keep going and I appreciate the opportunity. What I'm going to do then is for [Indiscernible 00:39:58], I am just going to put on the record that we have the same situation with adverse events due to comorbidities and also the unassessable reports. The next one, Latuda, we also had an unusable-- It was-- It included one death. All right, I'll let that one-- So, it's the same issue. What we're seeing is the pattern continues, it's just-- It's the same pattern. And my--

Dr. Kim: If I may interject, I just want to correct, these are not unusable cases. I think we are-- We potentially squash the reporter's voice when we say it. They're just unassessable when it comes to causality.

Ms. Oster: And that's the-- Okay, so for the record, just-- We need to-- I love the idea that the other person said, we need to figure out how to address this, right? I just want to go on record that I love the idea that the other doctor had mentioned, which is maybe that's a follow up for us. Okay. For-- Let me just see where I have-- Oh, can you comment on when you're doing your literature searches-- And I was looking at the drug, it was Liletta, were there any inclusions of lawsuits in the review? And then how can you look at lawsuits as possible information? And I believe that what I heard earlier today is that they're obligated to put that into the FAERS database, if you can just confirm I have that correct.

Dr. Kim: Yeah, so thanks again for the question. So, we review adverse events in FAERS. We don't necessarily review lawsuits, like legal dockets per se, but some litigation issues are reported into FAERS, so someone reports them into FAERS, and that data we review. The data standards for submission are the same as the other reports. There's a reporter, a patient, a drug, and an adverse event.

But when we analyze these cases, we also apply the same scientific standards for pharmacovigilance analysis. So, the short answer is yes, we review lawsuit cases, but only as they are entered into FAERS.

Ms. Oster: Okay. And then for the next drug, the N-I-T-Y-R, I just wanted to just comment here that 67% of the reports were again for the comorbidities and the concomitants. And again, I want to go on record in this case that this is an opportunity for us for improving, going forward. So, let me just see. Oh, and in this particular case, there was one death that lacked sufficient clinical information to understand the events. What process--? Or how can you get that information? Because just saying, "We couldn't get it" and that's how it reads to a consumer, it's not showing enough effort. So, can you just walk through, especially in the case of the death, what the process is?

Dr. Kim: Yeah, thank you. So, we do take all death reports pretty seriously. Those get extra screening, if you will, with routine pharmacovigilance as well. So, it goes back to what I was saying about the missingness of data. When possible, we get some structured data about where the report comes from. We try to get to the root data source. So, that could be a literature report, author, a study, and we're unfortunately not always able to obtain the data we need. So, sometimes-- I don't recall this particular report, but I'll speak generally in terms of death reports. When we say that there wasn't sufficient information to determine what the clinical event was, we're saying there truly was no information. It'll be something like "The patient died because he had medical issues and we don't-- That doesn't help us determine causality." So, unfortunately that's one of the limitations. And in this case, we weren't able to obtain more information. And those are activities we do as part of routine PV work in the background for all the activities we do, in and out of PAC.

Ms. Oster: We had the same information for Repatha, where there was also one death. So, we will move forward with that same answer, but there is definitely-- In the conclusion, I'd like to make sure there's opportunity here because, from a consumer point of view, it just seems the information should be available. So, I'm not sure how much effort is put in, I'm not saying there isn't, but perhaps we need to be

doing more. And again, that might be another discussion. Let me just go on to my next one. Okay, Stelara. Okay. In this case we had 30% of the reports were unassessable, and I had the same issue. At what point when people--? We had 19% of the people said it was a labeled adverse event. You were already looking at like 50% of the reports coming in, that I'm not saying you eliminate them, but they're not counting that, we're not getting new information that we can improve. So, for ongoing monitoring, I don't see how we would have changes. I think the next one-- Sutent. So, this case there was a warning and precaution for cardiovascular events and then there was a death. So, it's just-- So, how do we--? If someone-- Just because it says there's a possibility of death and then someone dies, can you comment on how do we really look at that from a lesson learned so as to prevent that?

Dr. Kim: Thanks for the question. I mean, this is similar again to our discussion of labeled events. So, irrespective of where that labeled event is, whether it's a box or a post-marketing event that's listed, we apply the same rigor, right? We're saying "Yes, there's this label, but are there features of it that make it more specific, more worrisome, or more specific to help inform clinical management?" So, part of the warnings and precautions is that there are cardiovascular events that can lead to fatalities. The case that we reviewed did not indicate that there were new features, it was more consistent with what we've already known, therefore we did not elevate it for discussion.

Ms. Oster: And then that's the same-- We're almost done. But T-A-S-I-G-N-A, in this case, there's a box warning about avoid use of concomitant drugs known to provide the QT interval and strong-- So, it's right on there, and then the case was not used because it was already in the warning. And so that's another concern. So, if it's a box warning and now they're still coming in with the issues, what do we do? At what point does it become a bigger issue for us to be evaluating to protect the consumer?

Dr. Kim: So, again, it's not not used. It's used in the review to determine if there's new features. So, the level which we escalated it is if there's new features showing that there is something more specific or increased severity or something that would help improve clinical management. So, if the report did not

indicate any of these features, we would not discuss it further. It did not present new information for us to discuss in regards to safety.

Ms. Oster: Okay. [Indiscernible 00:49:04.]

Dr. Fischer: Ms. Oster, you're breaking up a little bit.

Ms. Oster: Oh, I'm sorry. Can you hear me now?

Dr. Fischer: Yep, that's better.

Ms. Oster: Okay, thank you. So, for Topicort, there was a transplacental exposure. There were 18 cases, including 18 deaths. And there was limited data, not having clinical detail-- They had-- And so the question is: Just because we don't have the clinical detail, how do we vote “Yes” for something that we need to see as an issue? And what is the plan going forward that the FDA can use to increase safety when data is limited?

Dr. Kim: That's a great question. Thank you. So, I'll bring us back to the focus, which is new safety signals for pediatric patients. And when we say that we're talking about signals related to direct exposure to the drug product. Transplacental or prenatal exposure cases are a little bit different. We have to consider really complex interactions between maternal factors, fetal factors, environmental factors that can all lead to negative fetal or neonatal adverse events. So, because of that, that kind of evaluation is a little bit outside of the scope of the PAC reviews, partly because it would really require really different study methodology and different data sources. That's why we don't include these transplacental exposure cases in discussion. But like every other report we find with PAC reviews, we review every single one of them. Again, in terms of prenatal exposures, that doesn't mean we don't look at it. Remember that this is only part of the total pharmacovigilance program we do in FDA CDER, and part of routine pharmacovigilance, we are looking at these data in different ways with different data streams.

Ms. Oster: Okay. All right. Guess what? The last one I had was the X-Y-R-E-M and you've already-- It's the same issue again with the number of reports, and so you've answered that and I will assume that we don't need to go through and make you repeat it. But just for the record, we once again have an issue with unassessable data, and there were 449 reports and 448 were eliminated. So, you've explained this based on other ones, but those were my questions. And I really want to thank you for your patience and explanation.

Dr. Kim: Thank you for your questions. We really appreciated it, Ms. Oster.

Dr. Fischer: Okay. Any other questions from the PAC Committee? Please raise your hand if you have a question. All right, I don't see any hands raised. Dr. Kim, thank you so much.

Committee Discussion and Vote

Dr. Fischer: If there are no more clarifying questions here, we can go ahead and proceed with the voting for CDER. Next slide, please. There we go. And next slide.

The Voting Question that we're being asked about is, "The FDA recommends continuing routine, ongoing post-market safety monitoring for each of the products we just reviewed. Does the Pediatric Advisory Committee concur?" The options that you have are "Yes, No, Abstain or Recused." Are there any questions regarding the wording of this question? Raise your hand if you have any questions.

Okay, this is just a reminder to our public observers that the meeting is open for public observation, but the public attendees may not participate at this point unless specifically requested by the panel. If there are no further clarifying questions about the wording of this, we can go ahead and move to the vote. After the votes are collected, the vote will then be displayed on the screen and the Designated Federal Officer will read the vote from the screen into the record. PAC members will then have the opportunity to summarize their votes into the record and state any reasoning behind your vote. The voting will now commence, and it will just take a minute for them to set that up.

Okay. Welcome back, everyone. This is Gwenyth Fischer. We are ready to see the results if they could be displayed, and I will now turn the meeting over to the DFO.

Ms. Srivastava: Thank you, Dr. Fischer. This is Shivana Srivastava. For the voting question "Does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine, ongoing post-market safety monitoring for each of the CDER products under discussion?" The results are: for AUVI-Q Auto-Injector, there are nine yeses, zero nos, zero abstains, and zero recusals. For Diovan, there are eight yeses, one no, zero abstains, zero recusals. For Entresto, there are eight yeses, one no, zero abstains and zero recusals. For Eraxis, there are eight yeses, zero nos, zero abstains, and one recusal. For Eucrisa, there are seven yeses, one no, zero abstains, and one recusal. For Exjade, Jadenu / Jadenu Sprinkle, there are eight yeses, one no, zero abstains and zero recusals. For Fiasp, there are nine yeses, zero nos, zero abstains, and zero recusals. For Jakafi, Opzelura there are eight yeses, one no, zero abstains and zero recusals. For Latuda, there are eight yeses, one no, zero abstains and zero recusals. For Liletta, there are eight yeses, zero nos, one abstain, and zero recusals. For Mycamine, there are eight yeses, one no, zero abstains and zero recusals. For Nityr, there are eight yeses, one no, zero abstain and zero recusals. For Potassium Phosphates, there are eight yeses, zero nos, one abstain, and zero recusals. For Repatha, there are eight yeses, one no, zero abstains and zero recusals. For Rozlytrek, there are nine yeses, zero nos, zero abstains, and zero recusals. For Stelara, there are eight yeses, one no, zero abstains and zero recusals. For Sutent, there are seven yeses, one no, zero abstain, and one recusals . For Tasigna, there are eight yeses, one no, zero abstain, and zero recusals. For Topicort, there are eight yeses, one no, zero abstain and zero recusals. For Triumeq and Triumeq PD, there are nine yeses, zero nos, zero abstains, and zero recusals. For Xyrem, there are eight yeses, one no, zero abstains, and zero recusals. Thank you.

Dr. Fischer: Thank you. Now that voting for CDER has been completed, we will go down the meeting roster and have everyone who voted, please state their name, their vote, and if you want to, you can go ahead and state the reason why you voted as you did into the record. If you see an error, please correct it for the record. We'll start with Premchand Anne.

Dr. Anne: This is Dr. Anne. I voted “Yes” for all of the products that were discussed.

Dr. Fischer: Thank you. Douglas Diekema?

Dr. Diekema: Doug Diekema. I voted “Yes” for all products.

Dr. Fischer: Thank you. Charleta Guillory?

Dr. Guillory: Charleta Guillory. I voted “Yes” on all the products.

Dr. Fischer: Thank you. Sarah Hoehn?

Dr. Hoehn: Sarah Hoehn. I voted “Yes” on all the products.

Dr. Fischer: Thank you. Richard Holubkov?

Dr. Holubkov: This is Rich Holubkov. I voted “Yes” on all the products, with the exception of recusals for Eraxis, Eucrisa and Sutent.

Dr. Fischer: Thank you. Liza-Marie Johnson?

Dr. Johnson: This is Liza Johnson. I voted “Yes” for all products.

Dr. Fischer: Thank you. Gianna McMillan?

Dr. McMillan: Gigi McMillan. I voted “Yes” on all the products.

Dr. Fischer: Roberto Ortiz-Aguayo?

Dr. Ortiz-Aguayo: Roberto Ortiz-Aguayo. I voted “Yes” on all products.

Dr. Fischer: Randi Oster?

Ms. Oster: This is Randi Oster. I am the Consumer Representative. I voted "Yes" on several products. I'm not going to go through and explain my "No" votes, but I'll make a global statement that we need to look at how to improve missing data, concomitants and unassessable data for future ongoing studies, and the concept of having another session where we really start to look at what we can do to improve. I would say that the Consumer Representative is needed, and I hope the FDA hears that loud and clear. Thank you.

Closing Remarks and Adjournment

Dr. Fischer: Thank you, everyone, for your votes. Next slide, please. Okay, that wraps up our day here. Just to summarize, our PAC Committee voted to continue the current post-market surveillance on all the products presented to us today from CDRH, CBER and CDER after individual review and then Committee discussion. Thank you, FDA, for presenting this information to us as well.

A couple of important themes that came up today were around the challenges of getting data and the thorough but imperfect nature of that data. Both the FDA and the PAC acknowledged that the system can be challenging, both in terms of collecting the data and then also analyzing it in a systematic way. There was a recommendation from multiple PAC members that perhaps we should have a separate training session and discussion around the data collection itself as a more general topic separate from our review of individual products, and to focus on the monitoring as it is through that data.

So, thank you everyone for attending this. I'd like to thank all the individuals of the PAC team, and again, the FDA team members who spent their day presenting to us and answering questions. I'm now going to bring this meeting to a conclusion, and again, thank you for participating and thank you to the public for joining us. This meeting is now adjourned. Thank you.

Dr. Anne: Thank you.

Dr. Holubkov: Thank you.

[End of recording.]