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

Designated Federal Officer	Shivana Srivastava, RN, MS, PMP
Pediatric Advisory Committee Member, Chairperson	Gwenyth Fischer, MD
Pediatric Advisory Committee Member	Susan S. Baker, MD, PhD
Pediatric Advisory Committee Member	David Callahan, MD
Pediatric Advisory Committee Member	Douglas Diekema, MD, MPH
Pediatric Advisory Committee Member	Charleta Guillory, MD, MPH
Pediatric Advisory Committee Member	Steven Krug, MD
Pediatric Advisory Committee Member, Patient-Family Representative	Gianna McMillan, DBe, MFA
Pediatric Advisory Committee Member (Non-Voting), Industry Representative	Robert Nelson, MD, PhD
Pediatric Advisory Committee Temporary Voting Member	Premchand Anne, MD, MBA, MPH
Pediatric Advisory Committee Temporary Voting Member	Randall Flick, MD, MPH
Pediatric Advisory Committee Temporary Voting Member	K. Sarah Hoehn, MD, MBe
Pediatric Advisory Committee Temporary Voting Member	Liza-Marie Johnson, MD, MPH, MSB
Pediatric Advisory Committee Temporary Voting Member	Sandra Juul, MD, PhD
Pediatric Advisory Committee Temporary Voting Member	Jennifer Lee-Summers, MD
Pediatric Advisory Committee Temporary Voting Member	Wael Sayej, MD, MBA
FDA Participant	Prabha Viswanathan, MD, FAAP
FDA Participant	Mohamed Mohamoud, PharmD, MPH
FDA Participant	George Van Hare, MD
FDA Participant	Craig Zinderman, MD, MPH
FDA Participant	Ivone Kim, MD
FDA Participant	Anam Tariq, DO, MHS, FASN

Table of contents

Call to Order

Dr. Fischer: Alright, everyone. Good morning and welcome to today's meeting of the Pediatric Advisory Committee. I'd like to remind everyone to start to please mute yourselves in the Zoom platform and also on any telephone lines you're on when you are not speaking. For the media and press, please contact the HHS Press Room. Their website is www.hhs.gov/press-room/index.html and probably more easily, the telephone number 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 please direct all technical inquiries you may have to the AV Support Team at virtual-WOCC-Support@fda.hhs.gov. The slide you're seeing now displays the icon accessible for closed captioning today. Okay, next slide, please.

And good morning again, everyone. My name is Gwenyth Fischer. I will be chairing today's virtual meeting. I'm now going to call today's meeting of the Pediatric Advisory Committee to order.

The FDA has convened today's meeting to discuss the postmarketing pediatric-focused safety reviews that FDA has completed for several products across the three medical product centers: the Center for Drug Evaluation and Research, also known as CDER; the Center for Biologics Evaluation and Research, also known as CBER; and the Center for Devices and Radiological Health, known as CDRH. 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 FDA or by industry today. PAC members received the 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 today's meeting. Following a Question-Answer session and Committee discussion, the PAC will then 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 postmarketing safety and surveillance activities as reflected in the Agency's review documents. All other

matters pertaining to the use of the products under discussion, such as general development questions, are outside of the scope of today's meeting. Our goal is that today's meeting will be a fair and open forum for discussion of the plan 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 reminder, individuals will be allowed to speak into the record only if recognized by myself, and we look forward to a very productive meeting today. 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 only 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 until after its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

On behalf of the FDA, I thank all of you Committee members for your participation.

Introduction of the Committee

Dr. Fischer: Alright, we're going to start by going over the meeting roster here today as seen in the slide. I will 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 your role on this Panel.

I'll begin by introducing myself. My name is Gwenyth Fischer. I'm a Pediatric Critical Care Physician at the University of Minnesota. I'm an Associate Professor of Pediatric Critical Care. I also run the Pediatric Device Innovation Consortium at the University of Minnesota and I'm the Associate Chair for Research at the University of Minnesota. I'm also the Chair of this Committee. Next, we have Premchand Anne.

Dr. Premchand: Yeah, hi there. I'm Dr. Premchand Anne. I am a Pediatric Cardiologist and the Director of Pediatric Cardiology at Henry Ford St. John Children's Hospital in Detroit, Michigan. I'm a Temporary Member of the Pediatric Advisory Committee for this meeting.

Dr. Fischer: Thanks for joining us. Susan Baker.

Dr. Baker: Hi, I am Susan Baker. I'm a Tenured Professor at the University at Buffalo in the Department of Pediatrics. I'm a Pediatric Gastroenterologist and I'm a Member of the PAC.

Dr. Fischer: Thanks, Dr. Baker. David Callahan.

Dr. Callahan: Good morning. I'm David Callahan. I'm a Pediatric Neurologist, Professor of Neurology and Pediatrics at Washington University in St. Louis and St. Louis Children's Hospital.

Dr. Fischer: Thanks. Douglas Diekema.

Dr. Diekema: Good morning. I'm Doug Diekema. I am a Professor of Pediatrics at the University of Washington and a Pediatric Emergency Medicine Physician at Seattle Children's Hospital, where I also direct the Education at the Center for Pediatric Bioethics and I'm a Member of the PAC.

Dr. Fischer: Randall Flick.

Dr. Flick: Hi. Randy Flick. I'm a Professor of Anesthesiology and Pediatrics at Mayo Clinic, Pediatric Intensivist, Anesthesiologist, and I guess I'm an inactive Member of the PAC.

Dr. Fischer: Thanks, Dr. Flick. Charleta Guillory.

Dr. Guillory: My name is Charleta Guillory and I'm a Tenured Professor of Pediatrics at Baylor College of Medicine. I also direct the Neonatal-Perinatal Public Health Program at Texas Children's Hospital. I serve as a Member on this Committee.

Dr. Fischer: Thank you. Sarah Hoehn.

Dr. Hoehn: Hi, I am Sarah Hoehn. I do Pediatric Critical Care, Pediatric Hospice and Palliative Medicine, and a little bit of Gen Peds thrown in. I am affiliated with the University of Chicago Comer

Children's Hospital and then I'm also Chief Medical Officer at La Rabida Children's Hospital and I am a former member, now currently, I believe, a Temporary Voting Member of the PAC for today.

Dr. Fischer: Thanks for joining us. Liza-Marie Johnson.

Dr. Johnson: Good morning. [Indiscernible - 00:16:51] Johnson. I am an Associate Member in the Department of Oncology at St. Jude Children's Research Hospital and Director of our Bioethics Program. I am a Temporary Voting Member. Good morning.

Dr. Fischer: Good morning. Sandra Juul.

Dr. Juul: Sandra Juul. I'm a Professor of Pediatrics and Neonatology at the University of Washington. I'm also the Director of the Institute on Human Development and Disability at the University of Washington. And I believe I'm a Temporary Member of the PAC, but I'm not sure if I'm temporary or permanent. It's my first meeting.

Dr. Fischer: Welcome. Thank you. Steven Krug.

Dr. Krug: Hi, good morning. My name is Steven Krug. I'm a Pediatric Emergency Physician. I'm based at Lurie Children's Hospital in Chicago. I'm a Professor of Pediatrics at the Northwestern Feinberg School of Medicine and I'm a Voting Member of the PAC.

Dr. Fischer: Thank you. Jennifer Lee-Summers.

Dr. Lee-Summers: Hi, everyone. I'm Jenny Lee. I'm a Professor of Pediatric Anesthesiology at Johns Hopkins and I am a Temporary Member.

Dr. Fischer: Great. Gianna McMillan.

Dr. McMillan: Hi, I'm Gigi McMillan. I'm a PAC Member, Bioethicist with background in Family Support Programs in pediatric cancer. I've retired from teaching undergraduate and graduate Research Ethics and right now I'm the Chair of the Board of Directors for PRIM&R, Public Responsibility in Medicine & Research.

Dr. Fischer: Thank you. Robert Nelson.

Dr. Nelson Hi, good morning, Dr. Robert Nelson. I'm trained in Neonatology and Pediatric Critical Care, and I'm currently Executive Director of Pediatric Drug Development at Johnson & Johnson and I'm the Industry Representative to the PAC.

Dr. Fischer: Thank you. And Wael Sayej.

Dr. Sayej: Good morning, everyone. My name is Wael Sayej. I'm the Chief of Pediatric Gastroenterology at Baystate Children's Hospital and Subspecialty Center. I'm an Associate Professor at UMass Chan Medical School and I am a Pediatric Gastroenterologist. I'm serving today as a Temporary Member of the PAC.

Dr. Fischer: Great. Thank you all of you for joining us today and taking your time for these important topics. I'm now going to pass the meeting on to Shivana Srivastava to announce FDA representatives for today's meeting.

Ms. Srivastava: Hello, my name is Shivana Srivastava and I'm the Designated Federal Officer for today's meeting of the Pediatric Advisory Committee. Today's FDA speakers include doctors Prabha Viswanathan, Mohamed Mohamoud from the Office of Pediatric Therapeutics, Dr. George Van Hare 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.

Conflict of Interest Statement

Ms. Srivastava: The Food and Drug Administration is convening today, November 13th, 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 for which the Committee will discuss postmarketing safety events reported for these products.

With the exception of the Industry Representative, all Standing Members of the Committee are Special Government Employees 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 U.S.C., Section 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 U.S.C., Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. These 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 U.S.C., Section 208, Congress has authorized FDA to grant waivers to Special Government Employees and Regular Government Employees who have potential financial conflicts when it is determined that 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 interests reported by the Committee members, no conflict of interest waivers have been issued for this meeting.

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 Patient Representative is a Special Government Employee and, as such, has been screened for conflicts of interest. 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 or 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 products that are 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 17th, 2025 statement, FDA's only including Industry Representatives in Advisory Committee meetings where required by statute. FDA is required to include any Industry Representative in today's meeting under 21 U.S.C. 355(n)(r)(c). Under FDA's 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 debt 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 will now turn the meeting back to our Chair.

FDA Opening Remarks

Dr. Fischer: We will now proceed with opening remarks from Dr. Prabha Viswanathan, who is the Deputy Director of the Office of Pediatric Therapeutics, followed by an FDA background presentation by Dr. Mohamed Mohamoud, also from the Office of Pediatric Therapeutics.

Dr. Viswanathan: Thank you, Dr. Fischer, and good morning, everyone. It is my pleasure to welcome our Committee members and guests who are joining today's meeting of the Pediatric Advisory Committee. On behalf of my colleagues, I want to start by expressing gratitude to everyone involved in today's meeting. Thank you to our Committee members for their service and for the time they have taken to review the copious background materials that they received to prepare for today's meeting. Thank you to the FDA staff who made this meeting possible, including the teams who performed or contributed to the pediatric-focused postmarket safety reviews that are the subject of today's meeting, our speakers and center representatives, and all those who have contributed to the logistics and planning for today's meeting. I also want to thank the AV staff, both in the room and online, for their technical support today, and last but not least, I would like to thank the public for joining. Your presence and participation reflects your dedication to the health of our nation's children. Next slide, please.

The purpose of this brief opening presentation is to set the stage for a productive meeting. This is an overview of what I'll be covering, beginning with just a few announcements. Next slide, please.

Since our last meeting on July 9th, there have been no changes in the PAC roster and both a list of the PAC roster with the Standing Members as well as a full roster of today's meeting with the Temporary Voting Members is available with the meeting materials on the website. Again, thank you to all of you Standing and Temporary Voting Members for your service today.

From the FDA side, I'd like to share that Dr. Dionna Green departed the Agency in early October to pursue some new opportunities. Dr. Green served in a leadership capacity in the Office of Pediatric Therapeutics since 2018, initially serving as the Deputy Director before becoming Director in 2021. We thank her for her service and wish her all the best in her future endeavors. Next slide, please.

Next slide, please? Next slide, please. Thank you very much.

So, speaking of the future, we are excited to announce two upcoming pediatric-focused meetings that may be of interest to this audience. The first workshop is being convened on December 5th to discuss pediatric developmental safety with a focus on new approach methods. The second workshop is our 10th anniversary of the ADEPT series, which stands for Advancing the Development of Pediatric Therapeutics, and we're excited to mark this milestone with a discussion of neonatal product development, which we'll be discussing through the lens of rare disease frameworks. This meeting was initially scheduled for December, but will be likely postponed and information for registration and additional meeting information is available at the links on the slide. We'd like to also acknowledge our partners in the Triangle in Maryland, CERSIs, who are key partners in the execution of these meetings. Next slide, please.

Before we proceed with the focus of today's meeting, I'll provide an update on the Pediatric Research Equity Act, or PREA, non-compliance letters as required by legislation. FDA issues PREA non-compliance letters to sponsors if they fail to submit a required pediatric assessment or report of a molecularly targeted pediatric cancer investigation within the specified timeframe. FDA also issues such

letters if a sponsor fails 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 publishes the PREA non-compliance letters on our website as well as a sponsor's response with some redactions. If a sponsor has requested a deferral extension or submitted a waiver request by the due date, FDA does not issue a PREA non-compliance letter unless FDA subsequently denies the deferral extension or waiver request. Next slide, please.

Since the last reporting of non-compliance letters at the July 2025 Pediatric Advisory Committee meeting, there have been no new letters issued by CBER and seven new letters issued by CDER. For more information about all of these letters, you can please access the links on the previous slide. Next slide, please.

We'll now turn our focus to today's meeting. FDA has convened the Pediatric Advisory Committee to discuss pediatric-focused postmarket 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, please.

Before I discuss the agenda for today's meeting, I'd like to take a moment to reflect on the discussion from the last meeting on July 9th, and share some of the themes that we heard from the Committee, which we have also heard in prior meetings. Overall, missing data was the heart of individual's concerns that have been raised. These include missing variables in adverse event reports that were submitted to the FDA or incomplete capture of adverse event reports in other venues, for example, social media. For drugs, there were some members who were worried that the reports that FDA receives lack sufficient information to make a causality assessment. For vaccines, there were comments about the availability of data about concomitant administration both from premarket and postmarket data. And for Humanitarian Device Exemption products, which are by definition used by a very small number of patients, there were concerns about the small numbers and the ability to build context about why one or two reports might inform the broader use of that device. Also, with-- In the setting of Humanitarian

Device Exemption products, there were some comments about the learning curve that's needed for these devices that are used infrequently and the ability for individuals to share best practices among the small number of providers who participate. I do want to note that these are just examples of some of the viewpoints that were expressed in the past and are not representative of a consensus opinion of the Committee. Next slide, please.

With that in mind, this is a snapshot of our agenda for today's meeting. Following these remarks, my colleague Dr. Mohamoud will provide a background presentation summarizing FDA's Pediatric Safety and Monitoring Framework. The purpose of this presentation is to set the stage for a Committee's discussion regarding the optimization of pediatric adverse event reporting. We felt that that was an important component of today's meeting to address those concerns that were raised by the Committee and provide a forum for you to provide your recommendations to us for how we can work as an ecosystem involving all of the relevant stakeholders to improve reporting so that the FDA has all the core pieces of information needed to make a full causality assessment.

Following the discussion, we will break for lunch and the Open Public Hearing will begin as soon as we return at 1:15 p.m. Eastern time. We will then transition to a listing and discussion of the products evaluated in the pediatric postmarket safety reviews that were completed by the medical product centers: CDRH, CBER, and CDER. There's time allotted for clarifying questions and voting at specified times during the meeting. We are scheduled to adjourn the meeting at approximately 4:00 p.m. However, please do 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, please.

Discussion-- Next slide. Thank you. Discussion and voting procedures will be similar to those used in recent PAC meetings. There will be no vote on the first question of the morning. This will be for discussion purposes only. In the afternoon, we will use the Zoom platform to solicit a vote for each of the safety reviews under discussion today. The voting question and the answer choices will be same for all the centers and all the products. Each ballot will contain a series of voting questions, one for each of the

products listed on the ballot. The exception in the case of some of the CDER reviews is that sometimes CDER products were grouped into one pediatric-focused postmarket safety review and that same grouping will apply for voting purposes. Next slide, please.

This is a preview of the non-voting question that the Committee will discuss following the FDA background presentation. The question reads, “FDA encourages the public to submit adverse event reports when safety concerns arise. However, there are many factors that may impact reporting. What steps can patients or consumers, providers, and healthcare systems take to optimize the reporting of pediatric adverse events?” We look forward to hearing a robust discussion on this topic. Next slide, please.

This is a preview of the voting question for the afternoon, as well as an explanation of the answer choices. Those who have participated in several meetings recently will notice that we've expanded the language a little bit to reduce any ambiguity that might have been present in the past. The question reads as follows, “FDA did not identify new safety signals in the pediatric-focused postmarketing safety reviews conducted for the Pediatric Advisory Committee. As such, FDA recommends continuing routine, ongoing postmarket safety monitoring of each of the CDER, CDRH or CBER products under discussion. Does the Pediatric Advisory Committee concur?”

Voting Members will have the option to select from one of four voting choices. An answer of “yes” indicates that the Committee member believes that the pediatric adverse event reports have not identified a new potential safety signal and routine ongoing postmarket monitoring should continue. An answer of “no” indicates that the pediatric adverse event reports have identified a new potential safety signal and additional evaluation or surveillance should be considered to evaluate the specific signal, in addition to routine safety monitoring. Voting members have the option to abstain from a vote. One reason why folks might choose to abstain is if there's insufficient information to make a “yes” or “no” decision. And finally, there's the option to be recused from the vote. Voting members should select this option if they have been informed about potential conflicts of interests that have been identified on their pre-

meeting screening and all members have received a list of products for which they're recused from voting. Next slide, please.

During the vote itself, there will be some pauses in the meeting flow. Individuals who are trying to join the meeting while the Committee is voting or during the period of time that FDA's tabulating the vote will be placed in a waiting room and this process may take approximately 10 minutes or more. We thank you for your patience during that period of time. During this time also after the PAC members have completed casting their vote, there will be a short break while the FDA staff tabulate the votes. Once the meeting resumes, the vote results will be displayed and read into the record by the Designated Federal Officer. Afterwards, individual PAC members will be called upon to read their individual-- Their vote into the record, and provide any commentary that they desire to make.

That completes my opening remarks and I thank you for your time and attention. And I will now turn the podium over to my colleague Dr. Mohamoud for the FDA background presentation. Thank you.

FDA Presentation: Ensuring Safe and Effective Therapies for Children: FDA's Pediatric Safety Monitoring Framework

Dr. Mohamoud: Thank you, Prabha. Good morning, everyone. My name is Mohamed Mohamoud, Senior Clinical Analyst in the Office of Pediatric Therapeutics within the Office of the Chief Medical Officer at FDA. Today I'll be discussing FDA's Pediatric Safety Monitoring Framework focusing on the evolution of pediatric product development, our regulatory oversight, and the essential role of this Committee in ensuring the safety and effectiveness of medical products used in children. Next slide.

Our discussion today will center on four main objectives. First, we'll review the key legislation and regulatory processes that have shaped pediatric product development. Second, we'll highlight the role of the Pediatric Advisory Committee in advancing pediatric safety, and explain how pediatric-focused postmarketing safety reviews fit into the FDA's broader regulatory and public health framework. Third, we'll look at FDA's postmarket pediatric safety monitoring and signal detection framework, which, while

consistent with the approach used for adults, incorporates unique considerations for pediatric populations. Finally, we'll discuss FDA's ongoing initiatives to strengthen pediatric safety surveillance and encourage reporting of adverse events, both within the regulated community and among clinicians, caregivers and the public. The FDA greatly values the partnership of this Committee and today's presentation is intended to set the stage for your discussion, providing context on how these programs work together to protect children. Next slide.

Pediatric product development has evolved through several landmark laws, namely the Best Pharmaceutical for Children Act of 2002, or BPCA, Pediatric Research and Equity Act of 2003, or PREA, and the Pediatric Medical Device and Safety and Improvement Act, PMDSIA Act, of 2007. Next slide.

The BPCA Act of 2002 built upon earlier legislation, most notably the 1997 Food and Drug Administration Modernization Act, to strengthen the foundation for pediatric product development in the United States. BPCA established a voluntary incentive program designed to encourage pharmaceutical companies to conduct pediatric studies for drugs and biologics. Under this framework, manufacturers that complete FDA-requested pediatric studies may receive six months of additional market exclusivity. This Act also led to the creation of the Office of Pediatric Therapeutics, or OPT, which coordinates pediatric initiatives across the Agency. This Act also established a partnership between the National Institute of Child Health and Human Development at the NIH and FDA to support studies for on- and off-patent products ensuring the important information on dosing safety and efficacy in children is generated and shared.

Importantly, BPCA also included a requirement for pediatric-focused postmarketing safety reviews for drugs that receive pediatric market exclusivity. These reviews ensure that any new safety signals are identified and evaluated promptly following a pediatric labeling change. As this framework evolved, the Pediatric Advisory Committee, which had previously functioned as a Subcommittee of the Anti-Infective Drugs Advisory Committee became a standalone committee. Under the Food and Drug

Administration Safety and Innovation Act, the PAC was tasked with reviewing these postmarketing safety reviews 18 months after a pediatric labeling change. This marked the beginning of a more structured, transparent and collaborative process for pediatric safety oversight that continues today. Next slide, please.

The Pediatric Research Equity Act, PREA, enacted in 2003, complemented BPCA by making pediatric assessment mandatory for certain drugs and biologics. Unlike BPCA's voluntary approach, PREA requires companies to include data on pediatric safety and effectiveness whenever a product is likely to be used in children. PREA also formally established the Pediatric Advisory Committee to review safety information and advise FDA on research and labeling related to the pediatric population. Next slide, please.

BPCA and PREA work together but serve distinct purposes. PREA mandates studies, there's no reward, and they apply only to approved indications in adults. Certain orphan products are exempt. However, BPCA in contrast offers six months of additional exclusivity for voluntary conducted studies which may even expand indications or apply to orphan products. Together, these Acts ensure that both regulatory requirements and voluntary incentives drive pediatric product development and labeling. Next slide, please.

The goal of a successful development program is to make a product commercially available. Several things must come together in order for that to happen. When they do, the stars align and increase the probability that a drug or a biologic will be approved. Ultimately, the regulatory approval requires many things. For example, clinical data, adequate manufacturing, and many other factors which are out of the scope of this talk. Our talk today will focus on generating data to support the efficacy and safety of drugs and biologics and Humanitarian Use Devices. Next slide, please.

Pediatric product approvals, whether for drugs or biologics, are held to the same evidentiary standard as adult approvals. Under Section 505(d) of the Public Health Service Act, the substantial evidence of effectiveness must be based on adequate, well-controlled studies that are methodically sound,

statistically robust, and capable of distinguishing the true effects of a product from other influences. For pediatric drugs and biologics, this means demonstrating a clinically meaningful benefit such as an improvement in how a child feels, functions or survives, supported by comprehensive safety data collected throughout the development process. These data must also enable a meaningful risk-benefit assessment taken into account developmental physiology, growth patterns, and disease progression in children, which can differ significantly from adults. In other words, pediatric drug and biologic development must meet the same scientific and regulatory standards of rigor, but with an added focus on age-appropriate dosing, formulation and safety consideration. Next slide, please.

The Pediatric Medical Device Safety and Improvement Act of 2007 incorporated into FDAAA strengthened oversight for pediatric devices. It introduced a Humanitarian Device Exemption, or HDE program, designed for rare diseases affecting fewer than 8,000 individuals annually in the U.S. The PAC plays a key role here as well, conducting annual reviews of pediatric HDE approvals to ensure continued appropriateness and benefit for pediatric populations. Next slide, please.

The HDE approval process occurs in two steps. The device must first receive a Humanitarian Use Designation from the Office of Orphan Products and Development. Then, a Humanitarian Device Extension application is submitted to the Center for Devices and Radiological Health, or CDRH, or the Center for Biologics Evaluation and Research, CBER. Approval requires a reasonable assurance of safety and a probable benefit, but it's exempt from demonstrating full effectiveness. This is a critical flexibility for rare pediatric conditions where large trials might not be feasible. Next slide, please.

This slide illustrates the product development lifecycle for drugs, biologics, and medical devices, and how pediatric considerations are integrated at multiple points along the continuum. This process involves numerous FDA interactions including pre-IND or pre-IDE meetings, end of phase-- And end-of-phase discussions. Each of these milestones provide opportunities for early and ongoing input. During these interactions, sponsors and FDA review divisions collaborate and refine study design, develop age-

appropriate formulations, determine pediatric dosing strategies, and plan labeling-- And plan for labeling that accurately reflects the safe and effective use in children.

Importantly, safety data collection and monitoring occurs throughout every stage of the development process, from preclinical research and clinical trials through postmarketing surveillance. This continuous monitoring allows potential safety issues to be identified and addressed as early as possible. Once a product is approved, the vigilance continues with pediatric-focused postmarketing safety reviews that are reviewed by this Committee. However, it's important to note that postmarketing safety surveillance occurs for all FDA-regulated medical products regardless of whether these additional pediatric-focused safety review requirements apply. Every marketed product, adult or pediatric, is subject to continuous monitoring through Adverse Event Reporting System and FDA's Pharmacovigilance Program. In this way, the pediatric safety framework operates on two levels: a targeted legislatively mandated review process for eligible products with new pediatric labeling, and a broader continuous surveillance system that evaluates safety data for all products in real-world use. Together, these overlapping systems ensure that safety oversight is both comprehensive and sustained. Next slide, please.

Once a product has been approved, one of the most critical outcomes of that process is the prescription drug labeling, the official source of information for healthcare professionals and patients about the product's safe and effective use. Labeling reflects the culmination of all premarket clinical trial data reviewed by the Agency for any medical product. It communicates key details, such as dosing, administration and safety information. For pediatric products, labeling also plays an important role. It determines whether and how a product can be used in children, specifying age groups, weight-based dosing, and any difference in pharmacokinetics or adverse event profiles compared with adults. Ultimately, prescription drug labeling is not the end of the process. It's a living document that grows with our understanding of adult and pediatric safety and efficacy, and it's central to how we translate regulatory science into real-world protection for children. Next slide, please.

This slide provides a schematic overview of how FDA's pediatric labeling changes for drugs and biologics lead to postmarketing pediatric-focused safety reviews. When a new medical product regulated by CDER or CBER is approved, pediatric labeling may be absent or only partially developed. In these cases, FDA's review divisions engage in early discussions with the sponsor to evaluate the feasibility and timing of pediatric studies under BPCA and PREA. Based on those discussions, requirements for pediatric studies may be deferred to be completed after initial approval or in some cases waived when studies are not feasible or scientifically appropriate. Once those pediatric studies are completed, the data are reviewed by FDA and if the results support pediatric use, including at times negative studies, the product labeling is updated to include pediatric information.

This pediatric labeling change then triggers a mandated pediatric-focused postmarketing safety review, which occurs 18 months after the pediatric labeling change. The purpose of this review is to evaluate all adverse event data and ensure that no new or unexpected safety concerns have emerged since the product's pediatric labeling-- Pediatric labeling change. Meanwhile, safety-related labeling changes continue to occur throughout the product's lifecycle, informed by ongoing surveillance from multiple data sources. Together, this process illustrates how pediatric product oversight is continuous and adaptive, beginning at approval, extending through postmarketing monitoring, and culminating in a formal review by this Committee to ensure that products used in children remain safe and effective over time. Next slide, please.

As mentioned, when a product receives a pediatric labeling change, that triggers a postmarketing safety review under both BPCA and PREA requirements as we discussed, and after 18 months of such a change, the FDA is required to evaluate all adverse event reports related to that product and present the findings to the Pediatric Advisory Committee. Similarly, under the Pediatric Medical Device Safety and Improvement Act, the PAC is tasked with ensuring that Humanitarian Device Exemptions remain appropriate for the pediatric population for which it is approved. This process ensures transparency,

accountability, and ongoing vigilance in pediatric safety, and strengthens the collaboration between the FDA and the Pediatric Advisory Committee to safeguard pediatric patients. Next slide, please.

While the PAC scope is broad, one of the most important PAC responsibilities is to review pediatric-focused postmarketing safety data for drugs, biologics, and certain medical devices. These reviews rely primarily on passive surveillance data reported to the FDA. These systems are valuable for identifying potential safety signals, but they also have limitations, including under-reporting, variable report quality, and the inability to determine the true incidence rates of adverse events. Each review focuses on a defined period of time following a pediatric labeling change or approval, during which FDA evaluates all available adverse event reports and presents its findings to this Committee. However, it's important to recognize that this process represents only one component of FDA's broader pediatric safety monitoring efforts. Beyond the PAC review cycle, the Agency conducts continuous surveillance, engages in targeted observational studies, collaborates internationally, and implements new data-driven tools, all aimed at ensuring the ongoing safety of medical products used in children. Next slide, please.

So, pediatric-focused safety reviews encompass products overseen by all FDA medical product centers: CDER for drugs and therapeutic biologics, CBER for vaccines and biologics, and CDRH for pediatric devices under the HDE program. This multicenter effort allows for a holistic view of pediatric medical product safety. Next slide, please.

After a medical product is approved and begins widespread use, ongoing postmarketing safety surveillance becomes one of FDA's most important responsibilities. The postmarketing Adverse Event Reporting System is central to that effort. It allows FDA to monitor how medical products perform in the real-world setting and to identify any unexpected safety issues that might arise after approval. Reports of adverse events come from several key sources: healthcare professionals, who observe adverse events in their clinical practice; patients and caregivers, who may report directly through MedWatch, the FDA's voluntary online reporting system; and manufacturers, who are required by regulation to submit both expedited and periodic safety reports based on their ongoing postmarketing surveillance. Once these

reports are received, they are captured in product-specific internal FDA databases, such as the FDA Adverse Event Reporting System, or FAERS, for drugs and biologics, the Vaccine Adverse Event Reporting System for vaccines, and the Manufacturer and User Facility Device Experience, or MAUDE, database for medical devices. Next slide, please.

Manufacturers of drugs and biologics and devices are required to submit both expedited and periodic safety reports. Serious and unexpected or unlabeled adverse events must be reported promptly, while expected or labeled adverse events are compiled quarterly, then annually after three years of approval of the medical product. These reports are vital for signal detection, especially for rare or delayed onset adverse events in all populations. Next slide, please.

Passive surveillance systems like FAERS, VAERS and MAUDE are essential, but have strengths and limitations as we mentioned. They're particularly useful for identifying rare, serious, or early or occasionally delayed onset adverse events that may not emerge in clinical trials. However, they rely on report quality and completeness, making interpretation challenging when background rates of adverse events are high or reporting is inconsistent. Recognizing these constraints is key when evaluating safety data. Next slide.

The goal of a pediatric-focused safety review is to identify new safety signals, as we discussed. A safety signal arises when data suggests a potential new association or an unexpected aspect of a known risk. FDA assesses signals using factors like temporality, dose response, biological plausibility, and the absence of alternative explanation. The goal is to determine whether safety concerns warrant further investigation, regulatory action or labeling changes. Next slide.

When analyzing these passive surveillance databases, we look for patterns, clusters by age, dose, time, or event type that may indicate emerging safety concerns. These findings are crosschecked with other sources including literature and clinical trial data to confirm validity. Ultimately, this helps FDA and the Pediatric Advisory Committee make informed evidence-based recommendations for pediatric product safety. Next slide, please.

Once a product is approved and reaches the market, our work in monitoring its safety does not stop. In many ways, it begins a new continuous phase that occurs year around, outside pediatric-focused safety review process. FDA continuously collects and analyzes data from a range of postmarketing sources to detect and assess potential safety concerns that may not have been evident during premarketing studies. These sources include FDA's internal surveillance systems, as we mentioned, such as FAERS, VAERS, and MAUDE. In addition to these FDA-managed systems, we also utilize information from external and complimentary databases, such as the National Poison Data System and other real-world data sources like Sentinel for drugs and biologics or therapeutic biologics, and the Biologics Effectiveness and Safety Initiative for vaccines and biologics, and the National Evaluation System for Health Technology, or NEST, for devices.

FDA also reviews global safety data submitted by industry partners and collaborates with international regulators, including the European Medical Agency, EMA, to identify global trends that might affect U.S. pediatric populations. These diverse sources together provide a broad, nuanced view of real-world product performance, allowing us to see patterns, compare reporting rates, and place adverse events in the context of the overall product use. Next slide, please.

Safety signal detection begins with continuous surveillance of postmarketing databases, which is ongoing outside the pediatric-focused safety reviews for unusual patterns, such as unexpected increases in reports, clustering within certain age groups, or consistency across multiple reporting systems. Once a signal is detected, the next step is signal evaluation, where we assess whether the observed association is likely to be real and clinically meaningful. This involves examining temporality, whether the adverse event occurs in a plausible timeframe after exposure, dose response relationships, and biological plausibility, as well as alternative explanations such as underlying conditions or concomitant medications. If the evidence supports a credible relationship, we move to signal verification confirming the finding through additional data sources such as observational studies, manufacturer safety databases, or global pharmacovigilance networks.

This structured approach allows FDA to distinguish true safety risks from coincidental findings and to determine whether further regulatory action is needed, such as updating labeling, issuing a safety communication, or requesting additional studies. The PAC will be kept informed throughout this process and the PAC's input will be sought as warranted by the regulatory issue under consideration. Next slide, please.

FDA continues to strengthen reporting pathways through MedWatch online and mobile tools and simplified reporting forms and extensive outreach to clinicians, caregivers and professional societies. Transparency is equally important to the FDA. Platforms like FAERS's public dashboard provide open access to adverse event data, empowering the public to review and understand safety information. Next slide, please.

Beyond the formal Pediatric Advisory Committee process, FDA maintains a robust and continuously evolving system of pediatric-focused safety monitoring. These ongoing initiatives extend across the agency and operate year-round ensuring that pediatric medical product safety remains a top priority even outside the mandated 18-month review cycle.

To begin, FDA has assessed the impact of CDER mandated pediatric-focused safety reviews. In parallel, FDA has developed and implemented best practices for postmarket surveillance of human drugs and biologic products. These best practices guide FDA staff in how to consistently detect, assess, and manage safety signals. They emphasize proactive monitoring, cross-center collaboration and integration of premarket and postmarket data and early engagement when potential pediatric concerns emerge. The goal is to ensure that any potential risk to children are identified and addressed as early as possible. As part of our transparency commitment, FDA also publishes potential signals of serious risks identified through postmarketing surveillance. These are posted publicly on FDA's website to alert healthcare professionals and the public to safety issues that are under evaluation. This proactive communication allows clinicians, caregivers, and researchers to stay informed while formal regulatory reviews are ongoing.

Another important development is FDA's real-time adverse event reporting initiative. This initiative uses advanced analytics to identify changes in reporting trends almost as they happen. Real-time monitoring allows FDA scientists to detect potential safety concerns faster and initiate evaluations before signals escalate. These initiatives embody the shared mission of the FDA and this Committee to protect the health and the wellbeing of children through science-driven vigilance, responsiveness and transparency. Next slide, please.

So in summary, the FDA's work in pediatric safety really builds on a strong foundation of legislations like BPCA, PREA and PMDSIA. Together they ensure that studies in children are done responsibly and that safety continues to be monitored long after a product reaches the market. FDA developed a comprehensive framework that looks at the entire product lifecycle, from early development through postmarketing review, so that every decision keeps children's safety at the center. The Pediatric Advisory Committee plays a key role in this effort. Your expertise helps us identify emerging safety concerns and make sure that pediatric perspectives are always part of the conversation.

And finally, our commitment doesn't end there. Through transparency, outreach and public reporting tools like MedWatch and the FAERS public dashboard, we continue to encourage collaboration and awareness because protecting children's health is a shared responsibility. Thank you for your attention and continued collaboration. The work of this Committee is instrumental in protecting and advancing pediatric health. I welcome your questions and your discussion on any of these topics. Thank you. Next slide.

Q&A

Dr. Fischer: Thank you Dr. Mohamoud and Dr. Viswanathan for your presentations. Before we begin discussion on the non-voting question that we will discuss here shortly that the FDA has asked us to comment on, are there any clarifying questions for what was just presented about processes? And I

see a couple of hands up, so this is the time to ask as the FDA will not be participating in our PAC Committee discussion that will happen after this. So, Dr. McMillan, I see your hand up. Go ahead.

Dr. McMillan: Thank you. Thank you for such a comprehensive discussion, explanation about what goes on behind the scenes when you're collecting these reports. So, from a Committee member's point of view, so for example, in the list of drugs that we reviewed for this meeting, there's like roughly 1,200 unassessable reports that include 60 deaths. Now, as a Committee member, I am uncomfortable voting "Yes, continue what you're doing" with this incomplete information. And so I think that multiple times members of this Committee have brought up our unease with having being called upon to vote in a positive matter based on these sort of negative or unassessable reports.

And so I think for me personally, I don't know for the rest, but for me, I start going to problem-solving mode and very specifically, narrowly focusing on why do we have so many unassessable reports? Why are they incomplete? And so then I ask myself, "Is there a mission problem? Is there a communication problem? Is there a process problem?" So do all the reporters, the patients, consumers and healthcare professionals, do they understand the mission? Do they understand why we want this information and why it's important, and do they agree with that mission? Right? Secondly, is there a communication problem? Do they understand the requirements of reporting? Do they know how to do it? Do they know where to go? Do they understand the process? And then the third thing is the actual process. Is there something that could be done to the actual reporting process that's going to improve the quality of the final report? So for example, if it's a paper that they're filling out, and I don't think it is, are there enough check boxes to remind them to do all of these things? If it's web-based, which I assume it is, are there windows that they must fill in before they are allowed to go to the next screen or the next information item? So I mean, that's just like a real life hands-on-- I'm wondering, what is the process?

And I know from the outside looking in, there's quite a comprehensive process behind the scenes, but in the end, if I, as a Committee member, am required to vote on something and I don't have a complete set of data, and we're talking about lives, morbidities, deaths. That's, I think, why this question

has come up before. And so I think all of that-- Thank you for letting me get that off my chest. My question about the process is: Are there standardized reporting forms? I mean, I'm going-- Not mission, not communication because that's kind of "blah blah," but I mean the tactile, the actual hands-on, are there standardized reporting forms? And what could this Committee possibly do to assist you or give you ideas for improving the quality of the final reports?

Dr. Mohamoud: Thank you. Thank you so much for the question. I think you raised several issues that, I think-- We hope that during the non-voting discussion on the question that we posed to the Committee, that all these ideas that you brought forth what I think are all helpful, will help improve the process. Certainly-- Just to answer your specific question, yes, there are standard reporting forms for both, for drugs, for biologics and devices. There are required fields and non-required fields so a reporter doesn't have to fill the entire forms. Obviously, the forms are designed to try to get as much details as possible because the more details you have, the more informed decision you can make. But we know that that doesn't happen in all cases and there's constant efforts to look at these forms to see how you can balance, sort of simplifying the reporting process while at the same time capturing the most important elements that will help you make an informed decision. So, I think all of these factors weigh in, but I agree with you. I think communication, having standardized forms, making sure that we do more outreach, I think are all things that we certainly can work on and improve to make sure our message is heard loud and clear across all of healthcare.

Dr. Fischer: Dr. Viswanathan, do you have any additional comments?

Dr. Viswanathan: I don't. I welcome the question and it really beautifully sets the stage for this discussion and I'm really interested in hearing the feedback from all of the Committee members about what we can do to tackle this difficult issue. The more data that are reported to the FDA, the more robust the analysis can be. And as I mentioned, this really does take partnership from every element of the ecosystem so that people know how to report, they know what's important, what are those elements that we're looking for to really facilitate the causality assessment. And as my colleague just said, finding that

balance where there's enough information to make a robust report without becoming so burdensome that nobody wants to report. And so we want to hear from you about things that we can do in partnership with you to really achieve that balance.

Dr. Fischer: Thank you, Dr. McMillan. Other questions from the PAC? Go ahead and raise your hand if you have questions about what was just presented for Dr. Mohamoud and-- Ah, there's a question. Go ahead, Dr. Nelson.

Dr. Nelson: Yeah, thank you. Quick question. Years ago, when I was in clinical practice, I reported an adverse event in a neonate and actually received a telephone call from an FDA investigator wanting more information. Now I'm assuming that that must have been on their radar as something they were looking at, but I'm just curious how often-- I can imagine that's very resource-intensive and I suspect it's not done very often, but do you have any information as to whether or not FDA actively goes out and looks for more information under some circumstances and what would those be? Is that being done now? When I say years ago, we're talking 1990s, I have no idea if it's being done now or not. I'm just curious.

Dr. Mohamoud: Yes, thank you for the question. I think you're right on. I think we try to do this, obviously we don't do it on every report. We receive millions and millions of reports every year, specifically when talking about drugs and therapeutic biologics. But there is an effort to follow up with reporters. Reporters have to obviously leave the correct information for follow up, which doesn't always happen. But in the cases where it does happen and there is a serious concern about a particular adverse event, follow up does occur. I don't have sort of a rate to tell you how often that happens, but it happens for safety concerns that are serious and that FDA is potentially already investigating and is gathering more info, or desire to gather more information about. So, outreach does happen and it happens by phone or by email as well. Thank you.

Dr. Fischer: Thanks for that question. Dr. Guillory, go ahead with your question.

Dr. Guillory: First of all, Dr. Mohamoud, thank you so very much for that excellent comprehensive presentation, but I may have missed it. Could you tell me who are the primary people

reporting? In other words, is it the specialist, is it the primary medical home? Is it the hospitals? Who is actually reporting these adverse effects?

Dr. Mohamoud: Yes, thank you for the question. So, most of the reports that we receive come from regulated industry. And regulatory industry, by that I mean sponsors, whether they're sponsors of drugs, biologics or devices. And some of these reports might be submitted by healthcare professionals but submitted directly to the manufacturers, and then the manufacturers because they're required to report that information to the FDA, eventually that information gets to us. But there's also an ability for healthcare professionals to report to the FDA directly without going through the manufacturer, and that encompasses all kinds of healthcare professionals, physicians, pharmacists, nurse practitioners. So yeah, the list encompasses all healthcare professionals, and I don't have a sort of a number to say what healthcare professional or what specialty reports the most. So, I don't have that information, but the information comes from all healthcare professionals.

Dr. Guillory: May I have a follow-up, please?

Dr. Mohamoud: Yeah, please.

Dr. Guillory: Parents, how do parents who really know that there's an issue, how-- What's the process for a parent to get the information in?

Dr. Mohamoud: Yes, so we do have consumer reporting forms which are more simplified and use lay language to solicit information from patients. Speaking specifically about the pediatric population, obviously we get a lot of reports from caregivers or parents, not as much as we would like, but we get some of these reports, and we would like to get more and we hope that during our discussion you guys can provide us with perhaps some ideas so we can increase the number of reports that are coming directly from adolescents or coming through parents for younger children. But there are specific consumer reporting forms that use lay language and are designed to allow the public to report directly to the FDA.

Dr. Fischer: Thank you for all those great questions. I have a clarifying question as well. This is Gwen Fischer. So, you had mentioned that industry is mandated to report to you. In the case of them

finding out an adverse event directly or in the case of a provider calling or alerting them to an issue, what is the feedback loop there? So, how--What are the consequences for industry not reporting that and how is that monitored to ensure that that mandated reporting is occurring?

Dr. Mohamoud: Good question. Yeah, thank you for the question. I think-- You know, the FDA has regulations in place to require reporting and the reporting is required promptly for serious adverse events that are unlabeled, so unexpected, so things that we don't know about. So, these reports are required to be reported as promptly as possible so that we can address them. For reports that are sort of known, known risks of the drug and are already labeled, reporting doesn't have to happen as promptly and can happen periodically, and FDA sort of monitors that. As far as what type of enforcement, we constantly-- FDA has a sort of a compliance division that visits different sites and makes sure that adverse events that are reported within the facility within a particular company, that they have robust records for documenting those adverse events and relaying those adverse events to the FDA. Occasionally, I think something like that might happen where a company perhaps is delayed, and if that delay is legitimate, maybe the FDA will allow them some more time to build a more robust system and report that information. But in cases where there's clear negligence of reporting, obviously they can be admonished by a warning letter or maybe more severe action than that.

Dr. Fischer: Great, thank you. And then we have one more question for the clarifying question section of this discussion. Dr. Krug, go ahead. Dr. Krug, you're on mute.

Dr. Krug: Okay, there we go. Hi, can you hear me?

Dr. Fischer: Yes, we can.

Dr. Krug: So, this is Dr. Steve Krug, and I think we're sort of foreshadowing the discussion to follow, but getting providers and non-providers-- Providers, I mean healthcare providers, to report-- And we've learned this from just sort of safety event reporting at institutions. They need to understand what happens after they report and sort of understand how that sausage is made. And I'm not sure that that's evident to reporters because people are reporting locally. The reporting then by process or mandate

goes to the companies or sponsors and then eventually makes their way to the FDA, so there's a bit of a disconnect there. And I think if people understood how it worked and had these sort of stronger incentive about how things work and their potential impact, the good part of all of this, I think they might be more inclined to report because essentially they lodge a report and it goes into-- I don't want to call it a black hole, but it goes someplace and they never hear about it again. So, we have to talk more about how we bring this all together so that healthcare providers, patients, and families sort of better understand the important role that the FDA has and how this helps us to promote the innovation that we need to provide the appropriate therapeutics for kids and to be vigilant for safety concerns. Thanks

Dr. Fischer: Dr. Krug, those are all very relevant points to our next portion of this. So, I'll just ask you to repeat that when we get to a roll call in a minute on the open discussion part because I think that is very relevant to our next discussion. Thanks for bringing that up. Dr. Hoehn, do you have a clarifying question on the presentation? Otherwise I'll have you first up for our next section here.

Dr. Hoehn: Not sure. It could be either. It's about the topic of overdoses being a known-- Something that's listed, but then not necessarily anything that we're getting more information or prompts about. That's why I had a question from the content part of it, but my question, I guess for the process part of it, is even if overdoses are known risks, is there anything in the system that when someone's putting that in that gives them prompts or drops downs about whether or not Narcan was co-prescribed? So if hypothetically patient A took an overdose of medication B and it was a narcotic or an opioid, are there prompts built into the FDA system for them to ask additional questions about the co-prescribing of Narcan? I don't know which section that falls into, but it seemed process-related.

Dr. Mohamoud: Yeah, thank you. I mean, I can briefly respond to this question. So, whenever someone is reporting an adverse event, there are required elements that they are required to report, like the drug and the adverse event, like in this case it would be whatever drug it was, and the event would be an overdose. There's also an opportunity for free text reporting where you can describe as many details or as little details as possible. Obviously more details are encouraged, especially details that can help

establish an association between a drug and an adverse event. There's no specific prompts to prompt someone to say whether a rescue medication was given or not. But all that additional detail that can be provided in what we call the "narrative section" of the reporting form are all relevant because that gives to-- That gives an indication of the severity of the adverse event if a rescue medication was administered. Thank you.

Dr. Fischer: Thank you Dr. Mohamoud and Dr. Viswanathan for your great presentations here. We are going to move on to the next part of this discussion, so if we could move to the next slide, please. Thank you. Thanks again to both of our speakers and also for their clarifying answers to some of our questions.

PAC Committee Discussion on Non-Voting Question

Dr. Fischer: At this time, we're going to engage in an open discussion. It's on a non-voting question. This will be a general discussion about pediatric postmarket safety monitoring, and it's not intended to be focused on any specific products, including those that we'll be discussing this afternoon. So, this afternoon is a separate process. In your comments, please try to use general terms such as the type of drug, like a drug or a device or a biologic or therapeutic class. If you must refer to a specific product to illustrate your point, please try to use the generic name for the product and do not reference any products for which you have a potential conflict of interest.

Each member of the PAC will have the chance to provide their response, and I will be calling upon each of you to do so. I'll be asking for all PAC members to provide their perspectives on this important topic. As a reminder, the discussion is intended to be between just the PAC members and does not involve FDA staff. This is intended to be a discussion, so please raise your hand if you wish to make a statement in response to another PAC member's comments. I'd like to get through the roll call where all of you will have a chance to make a statement or some comments similar to what we were just doing. And

then once we get through everybody, we'll have an open discussion. Please go ahead and refer to other comments that have been made by PAC members and we'll try to stick to one topic at a time, if possible.

So the Committee discussion on non-voting question is the following: the FDA encourages the public to submit adverse event reports when safety concerns arise. However, there are many factors that may impact reporting, as we've been discussing. The question for us to discuss today: what steps can patients, consumers, providers, and healthcare systems take to optimize reporting of pediatric adverse events? So, I'm going to go ahead and go through our roll call and please make any initial comment and then we'll start with an open discussion. So, starting with Premchand Anne, please go ahead and turn your mic on and comment on the general question on the slide.

Dr. Anne: Thanks, Dr. Fischer. I'm Premchand Anne. I just had a couple of quick points and one of the things that was discussed earlier in the clarification time period was possible hard stops, you know, just implementing hard stops on a form to ensure the completeness of the submission. Along with those hard stops and the forms-- And I almost wonder, instead of just sending the adverse events to the company per se for the reporting, perhaps if there is a direct link between the FDA, whatever form it is, and the manufacturer site to submit that directly to both places. Just something to think about. The other thing that I think really does impact submission of these pediatric adverse events, of course, is the time. As a physician, there's more and more demands that are placed on the physicians, and this takes time, especially a detailed submission. While there is a significant emphasis on, and there should be, emphasis on patient welfare, pediatric patient welfare, the time does play a significant role also. So, I'll leave it at that.

Dr. Fischer: Thank you for those comments. Susan Baker.

Dr. Baker: Yes. I think that the previous speaker really addressed my concerns, physician time and really having hard stops with the input of data.

Dr. Fischer: Thank you. David Callahan.

Dr. Callahan: Yes. I guess my thought is that patients and the public would be encouraged to speak with their prescribing physician if they're going to fill out an adverse event just so that the physician can also be involved in making sure that it's reported appropriately with appropriate details.

Dr. Fischer: Great. Thank you. Douglas Diekema.

Dr. Diekema: Well, I would second what most people have said and would underscore Dr. Krug's earlier comments that I think for many of us, it's a bit of a black box. You don't know where those things go, if anybody looks at them and so on. And so I think for some providers there may be some questions about the utility of what they're doing. I mean, I have broader concerns about the quality and validity of the data, which aren't so much about reporting. I just don't know exactly what to do with data that doesn't have a denominator, and I don't know what to do with data that's very subjective. I mean, most of these drugs and devices are used in patients who have underlying conditions and it can be very difficult for a provider or a healthcare system to know whether it's the underlying disease of the drug. And so I think reporting is to some degree impacted by their own assessment as to what they think, which I think also raises some concerns about what to do with the data that's generated.

Dr. Fischer: Thank you, Dr. Diekema. Randall Flick.

Dr. Flick: Thank you. Randall Flick. So, the question is: what steps can patients, consumers, et cetera, et cetera, provide? And I think the real challenge here is what can the FDA do with the various stakeholders to improve reporting? Let me give you an example of what I'm thinking about here. It’s that this is a problem, having served on various Advisory Committees in the past, the access to accurate data plagues each of these Committees in their decision-making. The ability to make reporting more accessible, I think, is key. For example, the opportunity to work with Epic, for example. So each one of us in our daily work, if we have an adverse drug event, could simply go to an area of Epic to be able to report that. That's something that would make this process much simpler and I think provide better quality data. Unfortunately, like the past speaker, what we do with those data is a challenge. And having a repository or access to large databases, which are widely available now, to be able to query about

questions is really very important. And so if we get adverse drug reports, we have to have a large database to query to be able to make sense of those reports in real time, not next year or not next month, but really in real time. Thank you.

Dr. Fischer: Thank you, Dr. Flick. Dr. Guillory.

Dr. Guillory: Yes. The first thing I really want to have a better idea of is from the FDA, who are the reporters, and to get a percentage of that, so we will know specifically where and who we should be targeting. Because apparently it may be coming from one way, but I really worry about parents who are seeing this, and what happens to their reports if it goes through a physician and then a physician goes through a hospital. How is that information brought up? In terms of just in general, I think education. I never hear anything-- You hear about drugs, and very gently at the end of a commercial, you hear about all the complications. So, I always wonder how if you educate the public about these reports, would it be too many or would it be a scare tactic? I'm not sure, but whatever it is, I think parents who are taking care of the children and see the adverse effect should have an easy way of reporting this directly either to their physician when they're talking, but some sort of way where they can have access to reporting it directly to the FDA. So, I think more education, for sure, for parents, for the public, for physicians, and find out what we are doing in the hospital system as well.

Dr. Fischer: Thank you, Dr. Guillory. Dr. Hoehn.

Dr. Hoehn: Sarah Hoehn. So, I have three quick comments. I'll try and be quick. I know that we've talked about how to get more data, like Dr. Diekema was saying, but one potential idea that I know we've looked at with other medications in the past is looking at the number of prescriptions given, at least in the U.S., whether or not that would allow for a denominator to give a rate of some of these things.

And then the second point is that I think going through all the reports that we looked at, one of the things that I found, I don't know if the word is disappointing or frustrating, I mean it's understandable, but when we exclude the known adverse events, again going back to overdoses and things like that, I do worry that in the long term we're discouraging reporting because people will say, “Oh, well, we already

knew about that. I don't need to re-report it." But then if for some reason you start having much higher rates or an increased number, we wouldn't necessarily know because people would be discouraged from reporting because they would say that nothing ever changes. So, I think we do have to think about how we close the loop and that you do still want to know about known adverse events, particularly when it relates to fatalities around opioid usage and things like that, because I think it's really important that we're able to track that.

And then the third is I agreed with what everyone else was saying about easier reporting, whether it's an app or a different thing that's built in the EMR to make it more straightforward and then has the prompts in there so we can get meaningful data.

Dr. Fischer: Thank you, Dr. Hoehn. Dr. Johnson.

Dr. Johnson: Yes. The joys of being in the middle of the alphabet, people have said a lot of things. I think the answer to the question about where the reports were coming from, and it's mostly from the required reporting of sponsors, I think just shows a gap. I feel like the busy clinician is maybe always remembering or always hearing about vaccine adverse event reporting, but maybe they're not thinking of the FAERS database. So, I think clinician education, and then if you're going to do that and you're going to get more reports, the FDA is going to need more resources to go through them. I had also jotted down something about Epic. Maybe if there was some way that there was a release, there would be an easy way to either integrate or to report.

And then I think when-- I think in my capacity as an IRB Chair, sometimes I see these MedWatch reports that are attached to reportable events, but then the reportable event form that I'm seeing seems to have more nuance and context, right, than when I look at the MedWatch. It seems like there's not enough space or people don't write as much. And so potentially in the sort of era of smart forms and reporting, can you have something scalable so that if someone is reporting a potential adverse event that is a death, then it sort of takes you down one sort of smart pathway to get more information cause that's-- Not that sort of a minor rash isn't serious, but it would sort of also help, I don't know, make the data sort of more

nuanced and easier to look at, and then it might sort of encourage more information about those serious adverse-- Events that are more serious. I think that's about it for everything that I had scrawled down.

Dr. Fischer: Thank you, Dr. Johnson. Dr. Juul.

Dr. Juul: So, thank you. I was going down the pathway of helping people to realize that reporting is everyone's job. So, for drugs that parents administer to their children, if there could be like on the label or the material that they get when they pick up the drug, something about "If you have an adverse event, report here" with a website address. And similarly, for doctors that are in the hospital prescribing medications, having a spot probably on Epic to encourage them to report adverse events. And just talking about Epic, there is something called Cosmos that has accumulated Epic data from all the Epic sites in the country and in some other countries as well. So, there's millions and millions of data sets in Cosmos and that's available. So, that's all I've got.

Dr. Fischer: Thank you, Dr. Juul. Dr. Krug, I hope that you can reiterate your earlier comments.

Dr. Krug: Well, that would require a functional memory, but I'll try and summarize it. Just one quick thought, though. Hard stops are a great idea, but hard stops are also a barrier, so we have to sort of figure out the right balance there, in terms of the reporting tool. Many of us work in hospital systems and there are fairly robust adverse event safety event reporting systems. And I think that collectively the culture has changed, which should benefit this process. It has been my observation and experience that reporting increases when people sort of see an outcome and understand how important it is, of course. And I think that the current reporting mechanisms don't really allow you to do that because the outcome isn't necessarily even going to be visible at your institution. And since many of these reports are forwarded from your local reporting system to sponsors, I think that's where it sort of stops.

I think there are probably opportunities to align with not just with hospital-based systems and through hospital associations, but also through professional organizations, the American Academy of Pediatrics would be a good choice, to collaborate on a process by which we might better inform

healthcare providers and help them to understand why this is important, why we need this information, how is it used. And boy, it would be even greater for the system to provide some feedback to the reporters at least, even if it's just sort of a brief "Thank you." More difficult issues with the ultimate consumers who are not healthcare providers, although I agree with some of the comments that have been made.

Dr. Fischer: Thank you, Dr. Krug. Dr. Summers.

Dr. Lee-Summers: I agree with everything that's been said. What's coming to mind is that it would be good to reduce the burden on the patient and the patient's family. They have enough to deal with and we don't want to discourage them from needing to connect with their physician to do a joint complaint. So if the patient and their family file a report, I do think it should be the burden on the FDA to reach out to that physician to get additional information, specifically the questions that were listed earlier, such as the timeline of what happened, the physician may need to clarify something in the timeline that would or would not be interesting to the FDA. And several people have mentioned Epic. I think only 60% of hospitals are using Epic. And so if this was to roll out as something that would be easily reportable using the hospital's EMR, we would also need to make this available to the non-Epic hospital users just to make sure we don't get inadvertent bias.

Dr. Fischer: Thank you, Dr. Summers. Dr. McMillan.

Dr. McMillan: So, I'm keeping my thoughts very narrowed to just the reporting problem. And so remember I mentioned I wonder if there is a mission problem, communication, or a process problem. And I don't know. And before I could comment intelligently or try to brainstorm ways to improve, I think I would need more information about the shortcomings of each of those categories. So, how do we gather that information? Can we-- I mean, oh God, surveys. I hate surveys. But I mean, some way of reaching out to, let's say, I guess you could start with people who've already done some kind of reporting to ask them. "What's your understanding of why you did this and the importance of it? Was the communication regarding this process appropriate, and how exactly did the process work for you?" I mean, then you could have some immediate feedback from the people who are using it that might help us improve the

final quality of reports that we do receive. So, that's one thing. I would need more information about each of those things. The people who were to use the system to find out if there's ways-- What do they think--? Because what do they think, that needs to be improved, because we can't assume that we know what they need, right? We have to ask them what, from their experience, would be beneficial of any changes.

And then, the other thing I want to reiterate what a couple of people have already said, the question that you originally asked us is: What steps should be taken to get the people to report better or give a higher quality report? That should be reframed as: What can the FDA do to make it easy for them to give us full or quality reports? It's about us making it easy for them to give us the information that we need to make our decisions. I wonder-- We're talking about education and messaging like PSAs about the importance and what the process is, and how the final data is used to benefit the health of the public. Again, it's a money suck, but can we have some kind of formal PSA, like video or advertisement, something so that in general people understand that there is this postmarketing surveillance going on and it's very important for all of us to participate. Having been a parent, giving my child experimental or sometimes experimental, but other drugs at home during the course of his cancer treatment, parents really want to participate. Anything that we can do to be contributing to the treatment and care of our child, we're going to do it. And in fact, knowing that there's a way to report the information I have, because I'm the expert on my child when he's at home, so that is actually not going to be an onerous burden on parents, and in fact they would welcome it. It's just that we have to come up with a way to make it easy for them.

I think-- Again, this is education and messaging for each of the stakeholders as part of this reporting process. That each are going to require a different kind of messaging and a different kind of education, but it would be worthwhile to do it. And then finally, a big plus one for me on the denominator that would really help me understand the context of the decisions and the numbers that we're looking at, and the decisions we're making based on those numbers.

Dr. Fischer: Thank you. Dr. Nelson.

Dr. Nelson: Thanks. I just have one thing to add. I think one concern I have is figuring out, as people are talking about the flow of information, what are the potential barriers around confidentiality? So, for example, sponsors don't have access to patients and consumers unless they provide that information directly and get permission. I mean, you can't call a physician-- A physician is going to have to get permission to share information, et cetera. I just ask us to think through-- I mean, if it's all anonymized, that's fine, but if it's trying to follow up with insufficient information, then it can't be fully anonymized. I think we just need to think through the confidentiality issues that might arise and make sure we have solutions for that. It would be my only contribution to this discussion.

Dr. Fischer: Thank you, Dr. Nelson. And Dr. Sayej.

Dr. Sayej: Hi, everyone. Well, the advantage of being last is that everyone has already said everything I wanted to say. I kind of looked at this and broke it into three separate things. Who should be reporting? Where is this going to be reported? And who's going to follow up on it? Which is everything that everyone mentioned. I think patients, doctors, even pharmacists can be the people reporting this, obviously. If a patient picks up medication from a pharmacy, I think the pharmacy should be providing them with a reporting card. “If you have an adverse event, this is the number you call” or “This is the website that you go to report the adverse event,” and that should go back to the pharmacy and to the doctor eventually to follow up on it and from whatever the reporting number or the pharmacist should go to the FDA, and the FDA can be linked to the doctors or the pharmacist.

I think there's a process that can be put together there to ensure that there is a full circle in terms of where these reports are going. And then, once the report has been filed, the FDA can follow up with the people involved in this. The patient may be-- If they are reporting it, that means they want to be, most likely they want to be followed up with. They don't want to just be ignored about what happened to them. You can follow up with the primary care doctor and the primary care doctor can gain more information from the patient if needed. And that can protect the patient's privacy. So, I was recently trying to put an adverse event report on MedWatch, and it doesn't ask for patient name, it just asks for the date of birth

and the age, and protected information. So, it does protect the patient's confidentiality, but it doesn't really give you an option to who's going to follow up on this or how is this going to be followed up with.

And lastly, in the electronic medical records, as somebody mentioned something about EMR and how this can be linked to the EMR. So, if it gets reported to the doctor no matter which EMR they have, it would be nice to have something built in where you can just automatically report an adverse event and that kind of triggers a flag with the FDA or with the company that produce the medication, although that's hard to track because of the generics and other medications, but it is just something that will trigger a flag that an adverse event has happened and this needs to be followed.

So, I think there's a lot of work to do in terms of ensuring this happens. I have a patient right now that we recently admitted with a rare side effect from a class of medications that we're trying to report this. And in the hospital, honestly, nobody even thought about it until I mentioned something about it. So, it's not a very common thing that people kind of say, “Oh yeah, adverse event, we need to report it.” It doesn't come to their mind. So, I think educating providers, educating patients, educating pharmacists, educating hospitals, I think it's very important in terms of really getting a lot of these reported cases. That's it. Thank you.

Dr. Fischer: Thank you so much. I'm going to just attempt to summarize all these amazing thoughts and ideas here. And then, Dr. Juul, we'll get to your question or comment in just a second.

Based on the information you guys have all just shared, I separated this into a few different large categories here. The first is the form as a place for potential improvement. Items like, can it be tracked by hospital systems or attached to the adverse events programs that hospital systems already have? Is there a way to organize it and make it a little bit smarter such that it is less onerous on the person putting it in, but also characterizes the most important data? Would there be a way to tier that form such that events that were high harm events would be flagged and require more information when putting them in? And there were a lot of other good ideas about the form, which, just my 2 cents, perhaps there's an opportunity here

for the FDA to work with some or all of this Committee to review the form itself or potentially use a survey as someone mentioned to highlight how that might be improved.

The second category that came up was parent education and participation, and provider education. There were notes about how we can educate people with PSAs, get the providers more involved. There were comments about how parents might be able to participate a little bit better in conjunction with their physician provider and other ways that we might be able to educate the public on this. My additional comments on that subject, I do think that we're missing out on some non-physician reporting, such as our advanced practice colleagues, our trainees in particular. Residency education might be a standardized place to introduce some of this. And then, opportunities for other non-physician providers such as respiratory therapists, nurses, education along those fronts.

Moving on to the third topic, which was the EMR. A lot of great comments about how we might be able to integrate the EMR into this. That would also benefit us in having more real time reporting. It might be able to pull in more detail. Someone mentioned some smart tools specifically in the program Epic. My only additional comment to that is that the FDA may have immediate access to the VA system and recognizing that this is probably an issue far beyond just us here in pediatrics, whether or not the VA might be a place to trial an EMR coordination across the FDA and the EMR.

The fourth category that we all were speaking about was the accuracy of data. And I think this is probably the most complex one to address, but a lot of great ideas about how to improve the denominator, which has come up at multiple meetings that we've had for the PAC. Ideas included, tying that to prescriptions and hospital orders, how a pharmacy might participate in that as well. And so, I think that's another really great topic of discussion.

The only one addition I'll make on top of these categories is very specific to medical devices, and that is the universal tags, the UDIs that are now on all medical devices that label each medical device. I know that the FDA has a very robust system for tracking those. My impression as a provider is that hospitals do not have great infrastructure for tracking what happens to those on their end. And I certainly

don't think most hospitals are using that to track adverse events, but that might be another opportunity for hospitals to learn how to workflow a UDI, the badge that each medical device has, how they can track that and tag for adverse events. I certainly think that many institutions could benefit from education on how to implement that seamlessly into their current workflow.

So, that's the summary. Feel free to put your hands up and we can now have an open discussion on all of these things. Dr. Juul, go ahead.

Dr. Juul: Yeah, I was just going to-- So, at the risk of being booed out of the room, physicians at hospitals are required to do many different educational modules and having one about FDA reporting would serve to educate all prescribers at a given hospital. So, we're required to do stuff on asbestos and universal precautions, and opioid use, et cetera. So, we could add one about FDA reporting and the importance of it.

Dr. Fischer: Thanks, Dr. Juul. Any other comments, questions, thoughts about that particular subject before we move on? Okay.

Dr. McMillan: Actually, yes, I do. I'm sorry, I'm late finding my right button. So, related to that, if for example-- I don't know if this is exactly what she was talking about, but if for example, there was a ground round, a grand round presentation about FDA reporting or something like that, I always think that if you bring in a patient story as part of the information that you're giving to make your point, it's going to be a stickier message. I would promote the idea of using some personal narratives that illustrate these points, even when trying to educate the healthcare providers. It sticks a little better and I think it puts a human face on what we're trying to do, which is to improve the outcome for the general public as they take these drugs.

Dr. Fischer: Thank you, Dr. McMillan. I think that's a really practical suggestion and patient stories are a great way to help make these types of training a little less dry. I'll just add that our residents go through monthly training on how to be doctors in the world, and to me, they're the most flexible in their ability to pivot and learn new things. And so, I would suggest that this training should start either in

medical school or residency while they're fresh and still able to learn new tricks. Dr. Flick, I think you were next. Go ahead.

Dr. Flick: Thank you. My previous comments, and thanks Jenny, for your reminder about Epic. So, I used Epic as an example, not as the sole potential. All of us live in a world where we have event reporting systems in our hospitals and we are encouraged internally to report events regardless of the type of event. Imagine that when you reported that event, that there was a query to report this to the FDA. So, is this reportable to the FDA? If that is clicked or chosen, then your EMR can fill out most of the form for you. All the background information that the FDA needs that they don't get in the current system would be automatically populated into that form and then it would go to the FDA. And then, imagine the next step is that the FDA could take that information and query Cosmos, Cosmos or whatever it is, it's got 300 million patients in it, and look for similar events. What we really, I think need to do is move beyond forms and into an electronic environment, an AI-driven environment that allows us to think a little bit bigger than we have in the past. Thank you.

Dr. Fischer: That's great, Dr. Flick. Thank you. Dr. Krug, I think you were next.

Dr. Krug: Hi, Steve Krug here. I don't think we would be booing the first commenter out of the room because while I think the world has brought many, many more requirements for healthcare providers, this is important because here we're trying to encourage the expansion of therapeutics and devices for use in children, but we of course want to do that safely and we have perhaps a flawed reporting mechanism. That's really problematic. I absolutely agree that we can improve education on this. I just literally finished my semi-annual, so we do it at least twice a year until somebody introduces something new that we have to do right away. And then the current group of things I looked at was how to use a fire extinguisher, which I've seen at least five or six times before, and it's very important information, but this is also important. I think that there's a clear partnership opportunity between the FDA, sponsors and healthcare providers here to improve our awareness.

I also agree that we should be educating trainees. The problem there is that it's really hard to get your foot in that door because most residency program directors will tell you that there's no space or time to teach them something else, but this is a fundamental perpetuating behavior, therefore it needs to be part of their education. I think we can do so much more and help people to understand how this works. I love the idea of Dr. Flick about having a checkbox there that would say, "Do you think the FDA ought to know about this?" And if checked "yes," maybe there are a few more questions. Again, I think anything we can do to go from the observer to the regulatory agency in a more direct manner will be useful. Thank you.

Dr. Fischer: Thank you, Dr. Krug. I think speaking for the FDA, these types of practical solutions are exactly what they were hoping to generate with this conversation. So, keep them going. I think Dr. Sayej, you were next.

Dr. Sayej: Yes. Just one thing to add. I think-- I usually, every couple of years, I usually talk to the residents about things like this, and I've given some talks to the residency programs, but if there's a way that the FDA can put together a presenter's slide set that doctors can actually use to do ground rounds at different hospitals or at their own hospital, I think people will be interested in that. I definitely know when we're talking about new medications or drug approvals and things like that, our Research Department is always interested in hearing about FDA processes and outcomes. So, if there's a slide set, I, one, would be definitely willing to do grand rounds on it to my hospital. But I think we need to deliver the right message. And I think that should come from the FDA, not from me.

Dr. Fischer: Thank you. And I think that's a really good point that this group might be a resource to the FDA as we are already very engaged and interested in this process, and we all represent a variety of different institutions. And so, we might be a good opportunity to try some things out and pilot things at our own institution. Not to volunteer everyone, but it's good to have a really involved group to begin with when you start a project like this. Dr. Johnson, I think you were next.

Dr. Johnson: Thank you. I just wanted to go back to one of the earlier comments in this section about [Indiscernible - 2:00:04] education, and it's seared into my brain that 18 inches from a sprinkler head, but it's maybe not as well seared into my brain about the mechanism for reporting. But we can't forget all of the, especially in the era of hospitalist medicine, all of the general pediatric clinics and family medicine clinics where they're not necessarily affiliated with an academic medical center and don't have to do mandatory training, or people who are maybe hired as in a consultant non-employee capacity who also don't do mandatory training, and recognizing potentially some of the-- How many hospital systems and there are other competing interests. Could the FDA or should the FDA partner with AAP, right? So, having sort of things at meetings or does the FDA have a booth at the AAP meeting where they provide information about reporting? Is it a board competency on maintenance of certification that do you understand adverse drug reporting? If your patient has an outcome, do you know what to do? They may or may not agree, but it wouldn't be hard to add sort of one question into the overall cycle or add one sort of sub bullet into a competency for clinicians, and also remembering how we're going to reach APRNs, PAs and nurse practitioners who are also seeing a lot of patients these days.

Dr. Fischer: Thank you, Dr. Johnson. I just want to highlight one thing you said, which was about involving our physician or provider organization such as the AAP and others. That's a second or third time that's come up. So, just want to point that out as a central suggestion that we've been circling around here as a group. Dr. Anne, I think you were next.

Dr. Anne: Yep. Just a quick comment. I am a Pediatric Residency Program Director and we actually require several AMA modules to be done. These are mandatory, including sleep information, on sleep professionalism, so on and so forth. I don't see why this could not be an opportunity to develop a module, whether it be through the AAP or the AMA, whatever it is, and go ahead and implement that as a mandatory exercise for the residents. And going back to what Dr. Krug and Dr. Sayej were saying, Dr. Johnson, I think that could be a grassroots movement.

Dr. Fischer: Thank you, Dr. Anne. And just highlighting the suggestion that someone else had about bringing a patient story in so it's more relevant in the eyes of the beholder, I think is a great idea. Dr. Guillory, I think you were next.

Dr. Guillory: I think most of what I was saying from education. I really appreciate the partnering with, for example, the AAP. But one other thing I want to mention, and it may be maybe a little bit out of this arena, but for me to get a medical license every couple of years at a state level, a medical board license, you have to have so many CME requirements. And I remember having to do one specifically on drug trafficking. So, having something like this that's a requirement, you have to take it. It may be something that you may want to just add on to the list of things that we already have mentioned that I appreciate.

Dr. Fischer: Thank you, Dr. Guillory. Great suggestion. Dr. Flick.

Dr. Flick: Thanks. Just to-- I want to circle back and address or comment on the need for a denominator, which has been mentioned on a couple of occasions. Passive reporting systems never have denominators except in the situation where you have a passive reporting system within a captured population, which would apply to something like Cosmo or Epic, or Cerner or one of these systems where if you report in that system, you know the population in which that report occurred and could then query into determine a denominator. And I think all of us here recognize how important it is to be able to determine incidents and prevalence of these kinds of events. So, just to make sure that we commented on the denominator part. Thank you.

Dr. Fischer: Oh, sorry. I was talking to myself here. I was just saying that I think the denominator has now come up a few times in this discussion. So, just highlighting that we all feel the accuracy of information relies on being able to understand the frequency of events out of total events. Dr. McMillan, go ahead.

Dr. McMillan: I want to sort of light a fire under all of us. Postmarketing surveillance relies on good reporting and it is a way that we are protecting the health of the public. So, you've got-- As it was

explained in the beginning of our meeting, there's this beautiful system that ends with imperfect reports. And I would say we should reframe this and refocus. We need to have good reports at the beginning of your beautiful system so that we can do what the beautiful system is designed to do. So, the conversation we're having right now about how we can get a better quality of report at the end is very, very important. And it is worth the investment to try these different things to improve the quality of the report, which is only going to improve the entire system. So, I just wanted to reframe it a little bit. The reports are so important that they should be the primary focus and then, they will feed into the big beautiful system that we have behind the scenes. And also, I just wanted to say I volunteer for anything that you need. If you need help, just let me know. As a parent, as a parent, you-

Dr. Fischer: -You've been recorded officially saying that now.

Dr. McMillan: Oh, shame on me. But I mean, as a parent who's been through a life-threatening illness with her child, I want good reports, right? So that my child's future and the future of other children are going to be better safeguarded.

Dr. Fischer: That's fantastic. Thank you. There's been a lot of discussion around accuracy of data and some of that can be improved with some changes to forms and things like that, and others will need to be education based. But I think many people in this group have suggested that the long-term plan here really needs to be a better integration with systems that already exist in the hospitals, including the EMR and adverse event reporting that are already happening there, possibly in more detail than the FDA is getting. I'll just add my 2 cents to that in that someone earlier suggested that a report that is submitted by industry on behalf of a provider that's reporting to industry, I would love to get a copy of that because I would love to trust but verify that my comments to industry are in fact getting relayed to the FDA.

One thing we have not covered in great detail in this discussion, which has been really fantastic, thank you everyone for your great participation here. I just want to make sure that we're touching on the parent part of this and if people have ideas and thoughts about how we can both better educate caregivers

on their important role in this and also ensure that they are able to participate and have a clear way to do so. Any comments on that? Dr. McMillan, go ahead.

Dr. McMillan: All right. So speaking from personal experience and also I worked with almost a thousand families whose children had brain tumors. So, I've got a lot of background information in my head. When parents are first dealing with the health issue with their child, there's a lot of information that is being thrown at them. But they need a tool, an educational tool that they can take home with them so they can look at it at another time when their brain is more able to process things. So, it's old school, but a brochure, a tactile-- Something they can put in their purse, their pocket, or have around on the table that doesn't require them to log in or go to a particular link. That is a good first line of education that explains what it is, how to do it, why it's important, and then maybe there's a website you can go to if you want more information, but I think something tactile is important.

Secondly, when parents are dealing with a significant or life-threatening illness, they really benefit from peer mentors, mentors who have been trained to help them come up with lists of questions that they should be asking their doctors or their research team. But mentor training is a good way to get important information to parents who are dealing with their children's issues. And those are my two thoughts.

Dr. Fischer: Thank you. Those are great. Dr. Krug. Did we lose you?

Dr. Krug: Sorry. Sorry. I'm technology challenged I guess. I work in an emergency department at a [Indiscernible - 02:09:50] children's hospital. And so, while I'm not the oncologist working with these families, I take care of a lot of families that present with acute care concerns. And I would-- This is a gross generalization, but I sort of see two extreme groups. There are these incredible super parents who apparently went to medical school, though they're not doctors, they're not nurses, yet they know everything and they have everything under control, and they understand the process in part because they've personally been involved in reporting of concerns, of a variety of concerns. Even those families I still think need a guide or support. And then, there are these families that are just overwhelmed

for a variety of reasons, including just life itself. But there may be health literacy issues, there may be language issues, there may be access to care issues, and those poor families are barely keeping up with the regimen if they're doing that at all. Expecting them to sort of be reliable reporters I think is challenging.

I'm hoping there's a best practice out there, somebody who has figured this out, because this is not unique to my institution or the place where I live because I think we need to provide better support to families. And this may then again, also fall upon the healthcare providers in the healthcare systems, but families see things that we don't see. And gosh, we need to see those things. We need a mechanism by which we can be aware of their collective experience because within that experience are things like adverse drug reactions that we never hear about. I'll stop there.

Dr. Fischer: Thank you, Dr. Krug. I think that's very well spoken. And just to tag onto that, one area that I think is a little tricky, but potentially important for us to address is adolescent reporting. Adolescents now interact with many drugs and devices on their own with minimal parental feedback or knowledge, frankly. Is there something unique that needs to happen when we talk about caregiver feedback? Is that a group that it's worthwhile to get information from or educate on? I'm thinking specifically of things like insulin pumps, children who are giving themselves their own injections, children on long-term medications. To your point, Dr. Krug, it may not be reporting things like rashes or fatigue or other adverse events. So, is there a way to directly pull them into this conversation? Dr. Guillory, go ahead.

Dr. Guillory: The only comment I want to say about that is when we work with that in terms of working with parents and making sure we are not overburdening them, we really need to keep in mind that many parents have a fear of the medical system in terms of if they report something, will that affect the care they receive? So, as we are coming up with whatever we come up with, make sure that we, whatever it is, address that, especially in different vulnerable populations.

Dr. Fischer: That's a great point Dr. Guillory. Thank you. Any other comments on caregivers or the patients themselves interacting with the safety monitoring system? Any other general comments

about anything we've discussed today? Any final thoughts for the FDA? [I'll] give you one last second here to contemplate. Okay. I don't see any other hands up, so I think-- This has been a fantastic discussion. I really appreciate everyone's participation here and really outside of the box thinking. We're going to go ahead and break for lunch now. Lunch will end at 1:15 Eastern Time, so you have a little break here. And please, Panel members remember that there should be no communication of the topics that we've discussed during the break amongst yourselves or with any members of the audience. And we'll see you again at 1:15. Thank you.

Open Public Hearing

Dr. Fischer: Okay. Welcome back, everyone. We can go ahead to the next slide. All right. At this time, we're going to open the public hearing session. Welcome to the Open Public Hearing. We'll have you state your name and your affiliation, if relevant to this meeting. The Food and Drug Administration believes that the agency and the public benefit from a transparent process that helps ensure that 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, its product or if known, any of its direct competitors. For example, this financial information may include a company or group's payment for your travel, lodging, or other expenses in connection with your attendance here at the meeting or grant money that your organization receives from the sponsor or competitor. Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial relationships to which you can add to 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 on 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 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 only speak when you're recognized by the chairperson. Thank you for your cooperation and at this time, if any member of the public who did not register in advance to speak at today's Open Public Hearing session, would like to speak today, please email PAC PAC@fda.hhs.gov.

Speaker number one, your audio looks like it's connected now, so you can go ahead and introduce yourself. Please, go ahead and state your name and the organization that you're representing for the record before speaking.

Ms. Merkle: Hi, my name is Katie Merkle. I don't have an organization. I am a mom and a former pediatric recipient of a deep brain stimulator. Hopefully everybody can hear me.

Dr. Fischer: I hear you. Great. Go ahead.

Ms. Merkle: Okay, so I was-- As I said, I was a former recipient of this device and I wanted to share what my long-term story looks like with the Committee here. We warn pregnant women about the dangers of medications and deli meats, but no one warns about the risk of implanted medical devices. Not the manufacturer, not the FDA and not the medical system. At no point before consenting to the surgery, nor at any time during the 17 years I lived with this full device implanted, was I ever warned that it could break down, disintegrate and cause irreversible harm.

Since 2003, the DBS system for dystonia has been approved for pediatric use. During that time, nearly every major insurer, clinic and manufacturer have consistently described it as reversible, removable, and safe for long-term implantation despite the absence of any long-term safety studies or material data. Meanwhile, FDA reports have documented installation loss, corrosion, and disintegration of the leads implanted in patients.

I was 21 when I tested those insurances with decades of presumed device retention ahead of me until the system began to fail, and in 2022 an explant was attempted. Next slide. During surgery, it was discovered that at least one intracranial lead had disintegrated leaving fragments permanently embedded in my brain and damage that cannot be monitored because MRI, the only imaging capable of detecting it, is now permanently foreclosed. The second lead remains fully implanted with no way to assess and no safe plan for exit. This has left me and my physicians in a diagnostic void. I live with a permanent neurological injury and presumed toxic inflammatory that cannot be mapped, monitored, or fully understood. And the consequences extend beyond the patient. I carried a pregnancy while the device was presumed to be breaking down and yet there is no data on fetal exposure, no data on what it means for a child to be conceived, carried, and breastfed while an implanted device is deteriorating inside the mother's body. There are no established safe limits for these byproducts in neural tissue, much less fetal tissue, and there is no way to assure me as a mother that all this did not play a role in my daughter's delays. The manufacturer has remained silent and my FOIA request for this information still remains unanswered. Next slide.

The manufacturer has long known that its leads do degrade. Its own patents, testing, and regulatory recall history are established, yet the PMA required no degradation warning at all. The only required warning concerned material toxicity, and even that was never meaningfully disclosed. Next slide.

That warning appeared only in a patient post-op insert, something I never even saw until after 2022 and I went desperately looking for answers. Next slide.

During that search, I found the FDA's own databases contain reports describing the same patterns of degradation, insulation loss, and corrosion, yet these were coded simply as malfunctions or breaks. Next slide.

The 2025 pediatric dataset added 261 new reported malfunctions after FDA review, which were mostly low-risk charging and battery issues. But even with those corrections, the data still only tells part of the story because-- Next slide. The reporting window keeps shrinking. Some years include implants

back to 2001. Others erased everything before 2005 and, as of this year, everything before 2010 is no longer displayed. So, long-term failures disappear when the timeframe changes and long-term pediatric implants disappear from view. Next slide.

Across from every dataset, lead degradation is absent, not tracked, not categorized, and effectively erased under label malfunction. To categorize this as a malfunction is a disservice to an entire premise of DBS. DBS safety depends on stable hardware. When the lead degrades, that safety model collapses. A degraded lead produces effects that cannot be seen, measured or monitored. And because degradation is not acknowledged as the risk, clinicians have no framework to identify or evaluate it. The dozens of doctors I've spoken with have only recognized it in the OR because there is no warning, no category, no pathway for this failure. These risks cannot be assessed when no one has ever acknowledged that the device can fail in the first place.

I would like to ask this Committee to recommend to the FDA and CDRH an open MAUDE and postmarket reports to independent review, to ask manufacturers to clean up the coding by cause and to require clearer preoperative disclosure of lead breakdown. Because if physicians are never warned that leads can degrade and no one studies what happens when they do, the record will remain silent. Not because no harm occurred, but because no one was trained to see it.

One clear warning and one honest phrase would have preserved my right to choose. Instead, that promise was reversible-- Was proved irreversible. This was not a small mistake. It was a failure of the product, the oversight and the protections that should have stood between any patient and irreversible harm. The fact that a mother with a brain injury and no regulatory training could piece this together from the public paper trail is not an indictment of anyone. It is a sign that the system itself needs clearer tools, better data, and more live voices helping to inform it. Medicine and innovation can change lives, but without full disclosure, consent means nothing, and when that silence stands, the FDA fails the people it was created to protect. Thank you for listening and I appreciate any action you can take to help correct this problem.

Dr. Fischer: Thank you very much for sharing your presentation with us, the Advisory Committee and the FDA. We all appreciate the effort you took to come here today and share your story and your information. Do we have any other public speakers for the Open Public Hearing? Okay. If not, then we will go ahead and close the Open Public Hearing. I would like to remind everyone that there is a public docket that members of the public have provided comments on for today's meeting topics. They're posted publicly and you can access them on the FDA website. No further comments. I'd like to call the Open Public Hearing to a close and we'll continue with today's meeting agenda and transition to the discussion about pediatric-focused postmarket safety reviews completed by the Center for Devices and Radiological Health represented by Dr. George Van Hare. Go ahead, Dr. Van Hare.

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

Dr. Van Hare: Hi. Thank you, Dr. Fischer. For the record, my name is George Van Hare and I serve as a Medical Officer in the Office of Cardiovascular Devices at CDRH at FDA. I will now read a list of the CDRH regulated devices that are under discussion at today's meeting. First, there's the Enterra Therapy System. Second, there's the Contegra Pulmonary Valved Conduit. Third, there's Pleximmune Diagnostic System. And fourth, there is the Sonalleve MR-guided high-intensity focused ultrasound (MR-HIFU) system. Thank you. I will now transition the meeting back to Dr. Fischer, the PAC Chairperson.

Clarifying Questions

Dr. Fischer: Thank you, Dr. Van Hare. We'll now proceed with clarifying questions from the PAC. Remind you to use the raise hand button so that I know to call on you. When called upon, please remember to state your name for the record before asking your question and if we can just stick to one question at a time, and then any follow-on questions related to that subject just to keep things organized for Dr. Van Hare. We'll begin with individuals who submitted questions to the agency in advance to the

meeting. As a reminder, members can only ask questions or comment on products that they are cleared to discuss. If you have been recused from a product, you're not allowed to discuss this at the meeting. And don't see anyone, so we can go ahead and open the floor to any clarifying questions for Dr. Van Hare. Okay, Dr. Van Hare, it does not appear that we have any questions for you. Since there are no questions, we can go ahead and proceed with voting for CDRH.

Committee Discussion and Vote

Dr. Fischer: The voting question is now being displayed on your screen. It states: FDA did not identify any new safety signals in the pediatric-focused postmarketing safety reviews conducted for the Pediatric Advisory Committee. As such, FDA recommends continuing routine ongoing postmarket safety monitoring for each of the CDRH products under discussion. Does the Pediatric Advisory Committee concur? The options for us are "Yes," "No," "Abstain," or "Recuse" and you can see the definitions there on the slide. Are there any questions specifically regarding the wording of this question? If so, go ahead and raise your hand and I'll call on you. Okay. I don't see any questions. I again remind public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Do any members of the PAC have a comment or question that they would like to discuss with fellow Committee members before we begin voting? And Dr. Baker, I see your hand raised. Go ahead.

Dr. Baker: Yes. I was notified a few days ago that I am recused from voting on one of the items, so I'm just questioning how I would vote on all of them.

Ms. Srivastava: Hi, Dr. Baker. We'll cover that shortly. Just hold tight.

Dr. Fischer: Thanks for asking that, Dr. Baker. It'll become more clear when you see the voting tabulation. Any other questions? Okay, if there's no further discussion, we can go ahead now with the voting process. I'd like to add that after 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.

Dr. Fischer: Okay, sounds like we're ready to come back from break everyone. This is Gwenyth Fischer. We are ready to see the results if you could display them. 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 postmarket safety monitoring for each of the CDRH products under discussion? The results are: For Enterra Therapy System, there are 12 yeses, zero nos, zero abstains, and one recused. For Contegra Pulmonary Valved Conduit, there are 12 yeses, zero nos, zero abstains, and one recused. For Pleximmune, there are 13 yeses, zero nos, zero abstains, and zero recusals. For Sonalleve MR-HIFU, there are 12 yeses, zero nos, zero abstains, and one recusal. Thank you.

Dr. Fischer: Thank you. Now that the voting has been completed, we can go down the meeting roster and have everyone who voted please state your name, what you voted, and if you want to, you're welcome to state the reason why you voted as you did into the record. If you see an error with anything on the screen, please correct it for the record verbally. We will start with Premchand Anne.

Dr. Anne: Yeah, this is Dr. Anne. I voted “Yes, I concur” for four of the devices. I have no comments.

Dr. Fischer: Thank you. Susan Baker.

Dr. Baker: This is Susan Baker. I voted yes for two of the devices and I recused myself from two.

Dr. Fischer: Thank you. David Callahan.

Dr. Callahan: This is David Callahan. I voted yes on each of the four devices.

Dr. Fischer: Thank you. Doug Diekema.

Dr. Diekema: This is Doug Diekema. I voted yes on all four devices.

Dr. Fischer: Randall Flick.

Dr. Flick: Randall Flick. I voted yes on all four.

Dr. Fischer: Charleta Guillory.

Dr. Guillory: I voted-- This is Charleta Guillory. I voted yes on all four.

Dr. Fischer: Thank you. Sarah Hoehn.

Dr. Hoehn: Sarah Hoehn. I voted yes on all four.

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

Dr. Johnson: This is Liza-Marie Johnson. I voted yes on all four.

Dr. Fischer: Sandra Juul.

Dr. Juul: This is Sandra Juul. I voted yes on all four.

Dr. Fischer: Thank you. Steven Krug.

Dr. Krug: This is Steven Krug and I voted yes on all four devices. Thank you.

Dr. Fischer: Jennifer Lee-Summers.

Dr. Lee-Summers: This is Jennifer Lee-Summers. I voted yes on all four devices.

Dr. Fischer: Thank you. Gianna McMillan.

Dr. McMillan: This is Gianna McMillan. I voted yes on all four devices.

Dr. Fischer: And lastly, Wael Sayej.

Dr. Sayej: This is Wael Sayej. I voted “for” on all devices. I voted yes on all devices.

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

Dr. Fischer: Thank you. All right, thank you everybody. We can go ahead to the next slide. We're going to now transition over to a discussion about pediatric focus postmarket safety reviews completed by the Center for Biologics Evaluation and Research, and this will be represented by Dr. Craig Zinderman. Next slide, please. Go ahead, Dr. Zinderman.

Dr. Zinderman: Yeah, can you hear me?

Dr. Fischer: Yes, we can hear you now. Thank you.

Dr. Zinderman: Okay, great. Thanks. I had an audio problem. Okay, so hi everybody. Good afternoon. My name is Craig Zinderman. I am the Associate Director for Medical Policy in CBER's Office of Biostatistics and Pharmacovigilance, and I'm going to be reading the list of products which we're reviewing for the meeting today. Quelimmune, Sevenfact and Vaxchora. And I'll turn the meeting over back to Dr. Fischer. Next slide, please.

Clarifying Questions

Dr. Fischer: Great. Thank you, Dr. Zinderman. We now have an opportunity to ask clarifying questions from the FDA speaker, from the PAC. I'll remind you just to raise your hand and let us know who you are so I can call on you. As a reminder, members can only ask one question at a time or comment on products that they are clear to discuss. So, if you've been recused in this section, hold off on commenting please. I don't see any questions. I actually have one clarifying question for you, Dr. Zinderman. Regarding Sevenfact, which is an adolescent medication that I'm aware of that many people have prescribed off-label as is very common in pediatrics below the age of 12. How is that data used in reports and is it mandated for industry to provide that data if it's out of scope? Or-- I'm just curious what the process is for that.

Dr. Zinderman: I know good questions. It's not out of scope. So, the requirement to report adverse events applies to the sponsors, the manufacturers, for both serious and non-serious reports, and it doesn't matter what the use was, if it was off-label use or on-label use. They'll of course note in their report and their metric codes that we assigned to off-label use that the use is not consistent with the labeled indication, but the requirements still apply, even if it's off-label use. As far as the review on our end, those reports get included in the standard review that we do for all products on an ongoing basis. Again, regardless of the indication, it includes off-label use. So, we use the same procedures for weekly review of expedited reports and other direct reports, those reports that come directly from healthcare providers or consumers as they come in on an ongoing basis. And then, we also do periodic more in-depth reviews for each product. And so, that includes both on-label and off-label indications, both get considered when we do safety signal evaluation and then take regulatory actions in response to safety issues. We can also do that for off-label uses if there's a significant safety risk. We can do communications and other regulatory actions if appropriate, if we know that people are using products in a manner that's not consistent with the indication.

Dr. Fischer: Great, thank you for that. Dr. Hoehn, did you also have a question?

Dr. Hoehn: I had a question about the SCD, the Selective Cytopheretic Device. Is this the right time to ask that question? Yes?

Dr. Zinderman: Yes.

Dr. Hoehn: Okay, perfect. Sorry, Sarah Hoehn. Yeah, I had a question about how this is similar or different to plasmapheresis and if there's any comparison both in how it's tolerated hemodynamically or just sort of what the potential benefit would be? Because reading through it, it was hard for me to see how it would differ from currently tolerated plasmapheresis.

Dr. Zinderman: Yeah, so what's different about it from plasmapheresis is the selective binding of activated neutrophils and leukocytes. So, if you look at plasmapheresis, you're taking the plasma portion of-- Or plasma exchange therapy really. You're taking the plasma portion of blood and separating that

from the cellular components of the blood, and then you're returning cellular components back to the patient along with the crystalloid or colloid, and then-- So the plasma component and everything that's in it gets removed and doesn't get returned to the patient. And so, there are toxins, there are mediators, sometimes it's antibodies that you want to remove in that plasma portion, but that procedure is not selective, right? You're removing the whole plasma portion and replacing it with some sort of crystalloid and just the cellular components. Similarly, for leukapheresis you're removing the white blood cells from the blood usually because there's too much burden, like in the case of leukemia and there's too many-- Too much of a load of white blood cells and so you need to lower the number or you might want those white blood cells, you might want to extract them for further therapy like in the case of CAR T treatments where you're going to use those white blood cells for an autologous treatment after some further modification. But again, it's not selective for activated leukocytes, you're just removing the leukocytes for whatever you want. The reason that you want to do it.

In this case, this device is used to treat patients with acute kidney injury or pediatric patients with acute kidney injury and sepsis, and these patients can experience cytokine storm, hyper inflammation from activated neutrophils that release cytokines and other pro-inflammatory mediators, and that worsens outcomes in sepsis needing-- Sepsis with acute kidney injury that needs continuous renal replacement therapy. So, the cartridge part of the device has a filter-- Not a filter, a membrane that is designed to bind the most activated monocytes and neutrophils, so it removes them from the bloodstream and lowers the amount of inflammatory load and then resulting inflammatory mediators that these activated monocytes and leukocytes [Indiscernible - 00:46:56] create. So, you lower that inflammation and that's the intent to improve outcomes by that, you know, lowering that inflammation. So, that's the main difference.

As far as the hemodynamic load, we're not aware of differences in the hemodynamic load increases or decreases based on using this product compared to other procedures, and we haven't had any reports of that.

Dr. Hoehn: Thank you. My apologies if it was too basic, but that was very helpful, so thank you.

Dr. Fischer: Dr. Flick, do you have a question?

Dr. Flick: Yeah, just a quick one. I did notice on page three, there's a comment that the blood flow path in the SCD-PED is non-sterile. Am I confused there?

Dr. Zinderman: That is true. There is a part of the blood flow path here that's not sterile with this device. I can ask our colleagues from the Office of Therapeutic Products, I'm not sure if they're on. Dr. Tariq. If she's on, she can comment on that.

Dr. Tariq: Yes. Hi, good afternoon. Can you hear me okay?

Dr. Zinderman: Yes.

Dr. Tariq: Okay, great. Yes, there we go. So, the SCD device is basically a component of three parts. We've talked about the membrane, there's a cartridge and then there's one other design element. So, specifically the non-sterile part is the cartridge portion. While we have the tubing and the connectors and everything else, the synthetic portion of the cartridge, which is usually an off the shelf kind of hemodialysis filter cartridge that is actually manufactured by Fresenius. So, we basically use the same portion or the segment that Fresenius would often use in their thing, and it's connected to the CRT machine that these pediatric patients are on. Due to the non-sterile blood flow path of the SCD-P cartridge, the blood flow is in the device. Generally, we are monitoring for infections, but I will tell you in terms of the annual reports, we have not seen anything in terms of infection being a problem. I hope that helps clarify. Yeah.

Dr. Flick: I think so. It just struck me as a little odd and I wondered about the surveillance for infection, but thank you.

Dr. Tariq: Yeah, and just to add to the surveillance, we are actively monitoring for the surveillance on an annual report basis, but also if there's anything that happens immediately, they are to report it to the agency. So, thank you. Thank you for the question.

Dr. Fischer: Great. Any other clarifying questions for Dr. Zinderman? Okay, great. We can move on. Oh, Dr. Guillory, go ahead. Sorry about that.

Dr. Guillory: Yes, could we go back one slide please? My question, and I probably should know this. In terms of the cholera vaccine, do you monitor that outside the U.S. at all? Because I know there've been cholera outbreaks and I'm just trying to find out if that's used outside the U.S. and do we collect any of that data? Thank you.

Dr. Zinderman: Okay, so I don't recall offhand if the product is used outside-- If this product, this specific cholera vaccine is approved outside the U.S.. There are other cholera vaccines that are approved outside the U.S. This is the only cholera vaccine that's approved in the U.S. We do monitor any adverse event reports that we received in any-- Regardless of use, regardless of country. And again, just like the on-label vs. off-label discussion, it's the same thing. Regardless of where those events occurred, they would still have to be reported. If it's a serious and it's an unlabeled event, it still has to be reported to the FDA by the manufacturer within 15 days. And so, those would come into us, into VAERS and into FDA and CDC in the same adverse event reporting stream that all of our other vaccine reports get. And we look at all of the serious reports on a weekly basis. We do some screening of each report on a weekly basis and then again, a more in-depth periodic review-- Periodically for each vaccine. And that would include U.S., and foreign reports.

For VAERS itself reporting by healthcare providers and by doctors-- Sorry, healthcare providers and consumers that-- You can report to VAERS from a different country so we can get foreign reports, but generally we talked in the morning session about the difficulties with reporting and having people being interested in reporting and aware of reporting. We have troubles here. Having reporting in the U.S.,

reporting from outside the U.S. is of course far less and it's just a tiny fraction of the VAERS database in terms of non-manufacturer reports.

Dr. Fischer: Thank you, Dr. Guillory. Other questions for Dr. Zinderman about the biologics? Okay, now I think we can move to the next slide and we'll go ahead and proceed with voting for CBER just like we did for CDRH.

Committee Discussion and Vote

Dr. Fischer: The voting question is displayed on the screen. It states: FDA did not identify any new safety signals in the pediatric-focused postmarketing safety reviews conducted for the Pediatric Advisory Committee. As such, FDA recommends continuing routine, ongoing postmarket safety monitoring of each of the CBER products that we were just discussing. The question for you: Does the Pediatric Advisory Committee concur? Our options are “Yes,” “No,” “Abstain” or “Recused.” Are there any questions regarding specifically the wording of that question? If so, go ahead and raise your hand now.

I don't see any questions, so we can go ahead and I'm just going to remind public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Do any members of the PAC have a comment or question that they would like to discuss with fellow Committee members before we begin voting? Okay. I don't see any hands up so we can continue. We will go ahead now with the voting process. After the votes are collected, the vote will then be displayed on the screen just like last time, 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 can now commence.

Dr. Fischer: Welcome back everyone. This is Gwenyth Fischer and we are ready to see the results if they could go ahead and be displayed. I will now turn the meeting over to our DFO.

Ms. Srivastava: Thank you, Dr. Fischer. This is Shavana Srivastava. For the voting question, does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine ongoing postmarket safety monitoring for each of the CBER products under discussion? The results are: There are 12 yeses for Quelimmune, zero nos, zero abstains, and one recusal. For Sevenfact. There are 12 yeses, zero nos, zero abstains, and one recusal. For Vaxchora, there are 13 yeses, zero nos, zero abstains, and zero recusals. Thank you.

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

Dr. Anne: This is Dr. Premchand Anne. I voted yes for all three.

Dr. Fischer: Thank you. Susan Baker.

Dr. Baker: This is Susan Baker. I voted yes for Vaxchora, and I recused [myself] as directed for the other two.

Dr. Fischer: Thank you. David Callahan.

Dr. Callahan: This is David Callahan. I voted yes for each of the three products.

Dr. Fischer: Thank you. Doug Diekema.

Dr. Diekema: Yes. Doug Diekema. I voted yes for all three products.

Dr. Fischer: Thank you. Randall Flick.

Dr. Flick: Randall Flick. I voted yes for all three.

Dr. Fischer: Thank you. Charleta Guillory.

Dr. Guillory: Charleta Guillory. I voted yes on all three.

Dr. Fischer: Thank you. Sarah Hoehn.

Dr. Hoehn: Sarah Hoehn. I voted yes on all three.

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

Dr. Johnson: This is Liza Johnson. I voted yes on all three.

Dr. Fischer: Thank you. Sandra Juul.

Dr. Juul: This is Sandra Juul. I voted yes on all three products.

Dr. Fischer: Thank you. Steven Krug.

Dr. Krug: This is Steven Krug. I voted yes on all three products.

Dr. Fischer: Thank you. Jennifer Lee-Summers.

Dr. Lee-Summers: This is Jennifer Lee-Summers. I voted yes on all three.

Dr. Fischer: Thank you. Gianna McMillan.

Dr. McMillan: This is Gianna McMillan. I voted yes on all three.

Dr. Fischer: Thank you. And Wael Sayej.

Dr. Sayej: This is Wael Sayej. I voted yes on all three products.

Dr. Fischer: Thank you everyone. That wraps up our discussion about CBER and we can move on to the next slide.

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

Dr. Fischer: Great. We can now transition over to the discussion about pediatric-focused postmarket safety for reviews that were completed by the Center for Drug Evaluation and Research represented by Dr. Ivone Kim. As expected, this list is much longer. Go ahead, Dr. Kim. [Silence.] Dr. Kim, I see you but I can't hear you.

Dr. Kim: Hi, can you hear me now?

Dr. Fischer: Sure can. Perfect.

Dr. Kim: 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 FDA. I'll now read a list of CDER regulated products that are under discussion at today's meeting. Please note that I'll be stating trade names only, but as a reminder to the audience, both trade and generic names will be listed in the slides. And also note, please, that more than one product was included in the same review in some instances. So, products that were reviewed together are listed together in the slides and they will be voted on together at the conclusion of the Committee discussion. Next slide, please.

So, we have Abraxane. ArmonAir RespiClick, ArmonAir Digihaler, AirDuo RespiClick, AirDuo Digihaler. Aubagio. Austedo. Brexafemme. Bydureon, Bydureon BCise, Byetta. Cibinqo. Cosentyx. Descovy. Next slide, please. I am not sure if the slides are advancing. I can't tell from my end. Can someone confirm please?

Dr. Fischer: Yes, we're on Dupixent, it looks like, by the slides.

Dr. Kim: Thank you. So, Dupixent. Edurant, Edurant PED. Enbrel. Evotaz. Lialda. Linzess. Litfulo. Myrbetriq extended-release tablets, Myrbetriq granules. Nucynta, Nucynta ER. Opana. Next slide, please. Pifeltro, Delstrigo. Rapivab. Rexulti. Ryaltris. Selzentry. Simponi Aria. Smoflipid. Solosec. Taytulla. Tezspire. Next slide, please. Trintellix. Viibryd. Xofluza. Ycanth. Zegalogue. Zepatier. Zerbaxa, and Zosyn. Thank you. I'll now transition the meeting back to Dr. Fischer, PAC Chairperson.

Clarifying Questions

Dr. Fischer: Thank you. We will now proceed with clarifying questions from the PAC. Please remember to raise your hand using the hand button and also let us know who you are for the record before asking your question. Since there are so many products, if you can just be clear about which product you're referring to when you ask your question that will be helpful to the FDA. I don't see any questions yet.

So, while people are contemplating, Dr. Kim, I have a question about the duo inhalers or-- The breath-activated inhalers. I think this is probably a low risk for malfunction. When you have a drug and device. I know that when that device and drug are getting approved, you obviously treat it as a combination product and both Committees are involved. Is that true also for adverse effects when you're doing post safety monitoring?

Dr. Kim: Yeah, so what CDER covers usually is post safety monitoring, pharmacovigilance for drug safety, but we also looked at medication errors. Device issues can always come up and that's something that we look for and we work with our partners in CDRH in some cases to do complete evaluations should concerns arise.

Dr. Fischer: Thank you. The specific reason I'm asking is some of these inhalers, and I'm not specifically calling out any particular brand, but are known to have difficulty with the breath activation, especially for smaller patients and patients who can't necessarily adhere to instructions such as toddlers, but I would imagine that would be very difficult to tease out in terms of drug effectiveness versus effectiveness of the actual inhaler piece itself. So, I was just curious about that. Thank you. Dr. Hoehn, I think you were next.

Dr. Hoehn: Sarah Hoehn. I have a clarifying comment-- question about oxymorphone, which was number 19 on the slides and it goes to what we were talking about this morning in terms of what data is-- What we do with the data that's submitted. So, on page eight of the briefing documents, it says that four cases described death in a patient who had no exposure to oxymorphone and that four other cases described adolescent patients who died from accidental oxymorphone overdose, but that that was considered a labeled adverse event. I just think it would be helpful if there was a way for us to continue to track overall overdose deaths from sort of a public health perspective, which I do feel like is within the purview of the FDA. And again, we were talking about whether or not-- If we had prescription data of those who had accidental overdose, whether or not they were prophylactically at the same time they were given oxymorphone, were they also given naloxone as a preventative measure for safety? And I do feel

like in terms of the co-prescribing of reversal agents, for these meds being given to adolescent patients, there should be some way we can track that data. I guess, to turn it into a question, is there a way to track or get any additional details of the eight pediatric patients who had deaths reported?

Dr. Kim: Thank you for the question. I'll tease out a couple of nuances there. So, for the bullet point of excluded reports for discussion that says that the patient had no exposure to oxymorphone, I want to clarify. When we do these pediatric postmarketing pharmacovigilance reviews mouthful, we are doing a case level evaluation of every report that we retrieve. So, in those four death cases, we actually determined that the patient didn't have any oxymorphone. For some reason, they were miscoded as being exposed. That's why we don't discuss those further because the focus of the review was oxymorphone. For the other one, the labeled adverse event, I will say this is a little bit of an anomaly. Typically-- I mean, we always look at death cases a little bit more in depth and it's rare to have death listed as a labeled event, you know? But I like to remind you that we are reviewing, so they're not excluded from review. They are all being reviewed. And they are reviewed and those cases happen to be for overdose. We don't have tons of information just on this specific review, pharmacovigilance review for the purposes of the PAC, in terms of the trends for overdose overall. Not all of the reports or cases included information about full prescription of naloxone or the administration of the naloxone in the patient. I will say kind of alluding to some of the questions that came up in the morning part of the meeting that-- So, there are no hard stops necessarily for individual drugs in the FDA 3500 form that either consumers or healthcare practitioners can do turn in, but there is a section where patients can turn in report concomitant medications or other medications that they're prescribed. We just don't have the data to say that they were prescribed together at the same time.

Dr. Hoehn: Thank you. That's helpful.

Dr. Fischer: Dr. Flick.

Dr. Flick: Well, that comment just raised a separate question for me. So. if we have a death associated with a labeled event, should that prompt more rigorous vigilance even though it's an unexpected or labeled event?

Dr. Kim: Sure. Yes. Thank you for the question. So, when we look at an adverse event, of course we are excluding these cases specifically from the PAC reviews from further discussion. But again, we're not excluding them from review and whether it's a death outcome or a non-fatal outcome for any labeled adverse event, we're still looking for evidence of a new safety concern, right? Are there new features to the adverse event? Is it a new severity? There was a question earlier about are we tracking off-label use? So we're looking at all these factors and all these characteristics to see if there's new features to raise new concerns.

Dr. Flick: Okay, I think that helps. My original question related to ArmonAir and I saw in the briefing materials it says "Of note: ArmonAir has been discontinued from marketing." Was that a regulatory decision or a sponsor decision and was it related to safety?

Dr. Kim: The withdrawal from the market was not related to safety. The information should be available online, but I believe for ArmonAir, if I recall correctly, the withdrawal for marketing was requested by the manufacturer sponsor.

Dr. Flick: Okay. Thank you.

Dr. Fischer: Thanks for those questions. If anybody else has a question, go ahead and raise your hand now. Okay. I don't see anyone. Thank you, Dr. Kim. I think we can go ahead and proceed with voting for CDER.

Committee Discussion and Vote

Dr. Fischer: The voting question is again being displayed on your screen. It states that the FDA did not identify any new safety signals in the pediatric-focused postmarketing safety reviews conducted for the Pediatric Advisory Committee. As such, FDA recommends continuing routine, ongoing

postmarket safety monitoring of each of the CDER products under discussion. The question we are being asked to answer is, does the Pediatric Advisory Committee concur? And our options are “Yes,” “No,” “Abstain” or “Recused.” Are there any questions about the wording of the question before we continue? Okay. I remind our public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Do any of the PAC have a comment or question that they would like to discuss with the fellow Committee members before we begin voting? Go ahead and raise your hand if you have anything to discuss with the rest of the pack. Dr. McMillan, go ahead.

Dr. McMillan: So, I anticipate that I'll be voting yes on all of these, and I don't know where this comment should go in the record, but I'll just start with it now in case other people have a comment. So, three of these drugs, Zosyn, Dupixent, and Opana have a number of unassessable reports. So, for example, Zosyn has 54 unassessable reports, which is about 20%, and that includes two deaths. Dupixent has 994 unassessable reports, which includes nine deaths. Opana has 44 unassessable reports, which is about 20%. Oh, by the way, Dupixent 994 unassessable reports. It is more than two thirds of all of the reports. And then, Opana has 44 unassessable reports, which is about 20% which includes 33 deaths. So, while I understand we had a great conversation this morning, and while I imagine I'm going to vote yes that I recommend continuing routine monitoring, I can imagine a time in the not too far away future where I will not be willing to vote yes on these if we do not have better reporting data, especially when we're looking at 33 deaths within 44 unassessable reports. I just am uncomfortable with the lack of complete information that we are required then to vote on. And so, the answers would be-- The resolution to my particular dilemma would be if we came up with some new strategies for better reporting outcomes. Also, it could be that FDA staff needs to explain to me better how the context of all of these and what's the weight of the priorities and this number of-- What's the weight of the priority for this number of unassessable reports compared to the deaths, compared to all the reports collected. I mean, perhaps there's an explanation or a conversation that could be had to make me feel better. But I would like to know the

opinion of the rest of the Committee. And I feel like there is, like I said, a point in the future where I'm not going to be comfortable enough to continue just voting through these things based on incomplete reports.

Dr. Fischer: Thank you for those comments. Other PAC members, any other comments regarding Dr. McMillan's discussion or others? Dr. Krug. Go ahead.

Dr. Krug: Very elegantly stated by Dr. McMillan. I share her concerns. We need better data because in theory-- We are in part voting to continue monitoring of the drug, which is important, but the question becomes when does something that has a number of reported deaths in which we can't access data, where we take a different approach? So, again, [I] completely agree with Dr. McMillan.

Dr. Fischer: Thank you, Dr. Krug. I'll add that I definitely agree in general but just recognizing how hard it is to get data, especially in some of these complex patients who are on potentially several, many other therapeutics, potentially critically ill, that teasing that out even in a published research study is not complete and often has a lot of confounders. But I do think there are some things as we discussed this morning that perhaps could improve some of the data that we're getting. So, thank you everyone for those comments. Anybody else who'd like to speak to the PAC specifically? [Silence.] Great discussion guys. Thank you.

If there are no other comments, we can go ahead and begin the voting process. After the votes are collected, the vote will then be displayed on the screen just like last time, and the DFO will read the vote from the screen into the record. Then PAC members, you'll have another opportunity to summarize your votes and also state any reasoning behind your vote and we can go ahead with that process now. Thank you.

Dr. Fischer: Okay, welcome back everyone. This is Gwenyth Fischer and we are done with the voting process and are now ready to see the results if they could go ahead and be displayed on screen. And with that, I will turn the meeting over to our DFO.

Ms. Srivastava: Thank you, Dr. Fischer. This is Shavana Srivastava. For the voting question, does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine ongoing postmarket safety monitoring for each of the CDER products under discussion? The results are: For Abraxane, there are 10 yeses, zero nos, zero abstains, and two recusals. For ArmonAir RespiClick, ArmonAir Digihaler, AirDuo RespiClick, AirDuo Digihaler, there are 11 yeses, zero nos, one abstains, and zero recusals. For Aubagio, there are 11 yeses, zero nos, zero abstains, and one recusal. For Austedo, there are 12 yeses, zero nos, zero abstains, and zero recusals.

For Brexafemme, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Bydureon, Bydureon BCise, Byetta there are 12 yeses, zero nos, zero abstains, and zero recusals. For Cibinqo, there are 11 yeses, zero nos, zero abstains, and one recusal. For Cosentyx, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Descovy, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Dupixent, there are 11 yeses, zero nos, zero abstains, and one recusal. For Edurant, Edurant PED, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Enbrel, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Evotaz, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Lialda, there are 11 yeses, zero nos, zero abstains, and one recusal.

For Linzess, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Litfulo, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Myrbetriq extended-release tablets, Myrbetriq granules, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Nucynta, Nucynta ER, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Opana, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Pifeltro, Delstrigo there are 12 yeses, zero nos, zero abstains, and zero recusals. For Rapivab, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Rexulti, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Ryaltris, there are 11 yeses, zero nos, zero abstains, and one recusal.

For Selzentry, there are 12 yeses, zero, no, zero abstains, and zero recusals. For Simponi Aria, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Smoflipid, there are 12 yeses, zero nos,

zero abstains, and zero recusals. For Solosec, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Taytulla, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Tezspire, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Trintellix, there are 12 yeses, zero, no, zero abstains, and zero recusals. For Viibryd, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Xofluza, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Ycanth, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Zegalogue, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Zepatier, there are 12 yeses, zero nos, zero abstains, and zero recusals. For Zerbaxa, there are 12 yeses, zero no, zero abstains, and zero recusals. For Zosyn, there are 11 yeses, zero nos, zero abstains, and one recusal. Thank you.

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

Dr. Anne: This is Premchand Anne. I voted yes for all of the items.

Dr. Fischer: Thank you. David Callahan.

Dr. Callahan: This is David Callahan. I voted yes for each of the products.

Dr. Fischer: Thank you. Douglas Diekema.

Dr. Diekema: Doug Diekema. I voted yes for all items.

Dr. Fischer: Thank you. Randall Flick.

Dr. Flick: Randall Flick. I voted yes for all the items.

Dr. Fischer: Thank you. Charleta Guillory.

Dr. Guillory: This is Charleta Guillory, and I voted yes for all items.

Dr. Fischer: Thank you. Sarah Hoehn.

Dr. Hoehn: Sarah Hoehn. I voted yes for all items.

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

Dr. Johnson: Liza-Marie Johnson. I voted yes for everything, with the exception of the six products that I was recused on. Do you want me to list them out?

Dr. Fischer: No, I think that's okay. Thank you.

Dr. Johnson: Thank you.

Dr. Fischer: Thank you. Sandra Juul.

Dr. Juul: Sandra Juul. I voted yes on all items except for the two drugs that I was recused from.

Dr. Fischer. Thank you. Steven Krug.

Dr. Krug: Hi, this is Steve Krug. I voted yes for all of the products.

Dr. Fischer: Thank you. Jennifer Lee-Summers.

Dr. Lee-Summers: This is Jennifer Lee-Summers. I voted yes for all the products.

Dr. Fischer: Thank you. Gianna McMillan.

Dr. McMillan: This is Gianna McMillan. I voted yes on all the products, noting that I am comfortable doing so with the understanding that there will be meaningful exploration about how to improve the quality of the reporting mechanism.

Dr. Fischer: Thank you, Dr. McMillan. Can we go back to Dr. Flick. For one product you were abstained on? Just to clarify for the record.

Dr. Flick: That must be an error. I apologize.

Dr. Fischer: Okay, so correcting for the record.

Dr. Flick: It should be all yeses.

Dr. Fischer: All yeses. Okay. Thank you. And then finally, Wael Sayej.

Dr. Sayej: This is Wael Sayej. I voted yes for all products.

Closing Remarks and Adjournment

Dr. Fischer: Thank you everyone. We can go to the next slide. Well, thank you so much, everyone, for all of your hard work reviewing the materials as well as the very fantastic discussion that we were able to have this morning and further discussion and questions that we had this afternoon. You brought up a lot of very great points for the FDA as well, some really practical possible solutions as we move forward. I would like to thank the members of the PAC again for participating today, and as well as all the members of the FDA who were here today with us for providing the really great materials that we're able to review. And with that, I will bring this meeting to a conclusion. And again, thank you for all of your participation, everyone who's on this call, and we will now go ahead and adjourn the meeting.

Dr. Sayej: Thank you, Dr. Fischer. Thank you.

Dr. Fischer: Thanks all.