UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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Office of Clinical Policy & Programs

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PEDIATRIC ADVISORY COMMITTEE (PAC)

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10:00 a.m. EST

Via Web Conference

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Participants

Chairperson	Gwenyth Fischer, M.D.
Designated Federal Officer	Shivana Srivastava, RN, MS, PMP
Pediatric Advisory Committee Member	David Callahan, MD
Pediatric Advisory Committee Member	Angela Czaja, MD, MSc, PhD
Pediatric Advisory Committee Member	Douglas Diekema, MD, MPH
Pediatric Health Organization Representative (non-voting)	Jennifer Goldman, MD, MS
Pediatric Advisory Committee Member	Charleta Guillory, MD, MPH
Pediatric Advisory Committee Member	Richard Holubkov, PhD
Pediatric Advisory Committee Member	Bridgette Jones, MD, MS
Pediatric Advisory Committee Member	Steven Krug, MD
Patient-Family Representative	Gianna McMillan, DBe
Industry Representative (non-voting)	Robert Nelson, MD, PhD
Pediatric Advisory Committee Member	Roberto Ortiz-Aguayo, MD, MMM
Consumer Representative	Randi Oster, MBA
Pediatric Advisory Committee Member	Michael White, MD, PhD
FDA Participant	Dionna Green, MD, FCP
FDA Participant	Mohamed Mohamoud, PharmD, MPH
FDA Participant	Ivone Kim, MD
FDA Participant	Vasum Peiris, MD, MPH, FAAP, FACC, FASE
FDA Participant	Craig Zinderman, MD, MPH

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Call to Order

Dr. Fischer: Welcome, everyone. I'd first like to remind everyone to please mute yourselves in the Zoom platform, and if you're on a telephone line, to also mute that when you're not speaking. We'll begin with some just general announcements for media and press. The FDA press contact is April Grant. Her email is april.grant@fda.hhs.gov, and her telephone number is 202-657-8179. For members of the open public hearing industry and press, please sign in by sending an email to PAC@FDA.hhs.gov. Please direct all technical inquiries to the AV support team at virtual-WOCC-support@fda.hhs.gov. Okay, this slide displays the icon accessible for closed captioning today.

Good morning everyone. My name is Dr. Gwenyth Fischer and I am chairing today's virtual meeting. I will now call today's meeting of the Pediatric Advisory Committee to order. The FDA has convened today's meeting to discuss the post-marketing pediatric-focused safety reviews that FDA has completed for several products across the three medical product centers: the Center for Drug Evaluation and Research, known as CDER, the Center for Biologics Evaluation and Research, known as CBER, and the Center for Devices and Radiological Health, known as CDRH. The FDA's review of adverse event reports for the products under discussion today did not identify any new pediatric safety concerns. Therefore, no product-specific presentations will be made by the FDA or industry.

PAC members received FDA's review documents in advance of today's meeting to become familiar with the adverse events that were reported for these products and FDA's assessment of these events. The PAC will have the opportunity to ask the agency clarifying questions during this meeting. Following a Question-and-Answer session and committee discussion, the PAC will 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 post-marketing safety and surveillance activities, as reflected in the agency's review documents. Other matters pertaining to the use of the products under discussion, such as general development questions, are outside 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 toward topics beyond the stated scope of the meeting, I may, as chairperson refocus the discussion

as needed. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the FDA Advisory Committee Act and the government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you. On behalf of the FDA. I thank all the Committee members for their participation today.

Introduction of the Committee

Dr. Fischer: We are going to move on to introductions of the Committee panel members, and we're going to review the meeting roster as posted here. I ask all members of the Committee to turn on their cameras now and keep them on for the duration of roll call. When I call your name, please briefly introduce yourself with your primary area of expertise, institutional affiliation, and role on this panel. I'll begin by introducing myself.

My name is Gwenyth Fischer. I am a pediatric critical care and medical device specialist. I'm an associate professor of Pediatric Critical Care at the University of Minnesota and also the Division Chief of Pediatric Critical Care. I'm the associate director of the University of Minnesota Bakken Devices Center, and also the director of the Pediatric Device Innovation Consortium at the University of Minnesota. I also run the associate chair for research in the Pediatrics Department, and I am now the chair of the Pediatric Advisory Committee. Next we have Dr. David Callahan. Please go ahead and introduce yourself.

Dr. Callahan: Hello. I'm David Callahan. I'm a professor of Neurology and Pediatrics at Washington University School of Medicine in Saint Louis Children's Hospital, and I'm section head of General Pediatric Neurology.

Dr. Fischer: Thank you. Dr. Angela Czaja.

Dr. Czaja: Morning, everyone. My name is Angela Czaja and I'm a professor of Pediatrics and Critical Care Medicine here in the University of Colorado School of Medicine in Children's Hospital Colorado.

Dr. Fischer: Thank you. Douglas Diekema.

Dr. Diekema: Good morning. I'm Doug Diekema. I am a professor of Pediatrics with an adjunct appointment in Bioethics and Humanities at the University of Washington and practice pediatric emergency medicine at Seattle Children's Hospital. Chair of the Institutional Review Board there and I'm director of Education in our Center for Pediatric Bioethics. I'm a member of the PAC.

Dr. Fischer: Jennifer Goldman.

Dr. Goldman: Hello, I'm Jenn Goldman, I'm a pediatric infectious disease physician and clinical pharmacologist at Children's Mercy in Kansas City, and I serve as the Pediatric Health Organization representative.

Dr. Fischer: Charleta Guillory.

Charleta Guillory: I'm Charleta Guillory. I'm a professor of Pediatrics at Baylor College of Medicine and Texas Children's Hospital, and I'm in the section of neonatology, and I serve as the director of Neonatal Perinatal Public Health Program. I'm a member of this Committee.

Dr. Fischer: Richard Holubkov.

Dr. Holubkov: Hey. Good morning, all. I'm Rich Holubkov. I'm a clinical trialist. Biostatistician. I'm a professor based in Pediatric Critical Care at the University of Utah, working at a large coordinating center. And I am a PI-- Multiple PI for numerous trials focusing on surgical and cardiac interventions. Glad to be here. Thank you. PAC member.

Dr. Fischer: Bridgette Jones.

Bridgette Jones: Good morning. My name is Bridgette Jones. I'm professor of Pediatrics at University of Missouri-Kansas City School of Medicine. I'm a pediatric allergist and clinical pharmacologist at Children's Mercy Hospital in Kansas City.

Dr. Fischer: Steven Krug.

Steven Krug: Hey, good morning everybody. My name is Steven Krug. I am a pediatric emergency physician at Lurie Children's Hospital in Chicago. I'm a professor of Pediatrics at the Northwestern

University Feinberg School of Medicine. I'm the prior head of Emergency Medicine at Lurie Children's. And, I've done a lot of work in the emergency readiness and disaster readiness fields. Glad to be here today.

Dr. Fischer: Gianna McMillan.

Dr. McMillan: Good morning, everyone. I'm Dr. Gianna McMillan. I'm a bioethicist. I have just retired from teaching research ethics at Loyola Marymount University, but I am still in the game. I'm vice-chair, Board of PRIM&R, and a member of the North Star IRB.

Dr. Fischer: Robert Nelson.

Dr. Nelson: Yeah. Good morning. It's Dr. Nelson. I'm executive director of Pediatric Drug Development at Johnson and Johnson, and I'm the non-voting industry representative to the PAC.

Dr. Fischer: Roberto Ortiz-Aguayo.

Roberto Ortiz-Aguayo: Good morning. I'm Roberto Ortiz-Aguayo. I'm a pediatrician and child psychiatrist, and I'm the current chief of Psychiatry at Nemours Children's Health in Delaware Valley. And I specialize in complex pharmacology as well as systems of care. I'm a member of the PAC.

Dr. Fischer: Randi Oster. You're on mute, Randi.

Randi Oster: Hi. Sorry, I'm Randi Oster, I'm the consumer representative. I am a Medicare specialist. I work with consumers to navigate the health care system, and I am a member of the PAC.

Dr. Fischer: And Michael White.

Dr. White: Hi, I'm Michael White, I'm one of the PAC members. I'm a pediatric cardiologist at the Ochsner Health System, associate professor at the Ochsner University of Queensland Clinical School, chair of IRB, and vice-chair of our Clinical Ethics Committee.

Dr. Fischer: Excellent. Thank you everyone for joining the meeting today. I will now pass the meeting to Shivana Srivastava, who will introduce the FDA representatives for today's meeting.

Introduction of FDA Representatives

Shivana Srivastava: Good morning. Hello. My name is Shivana Srivastava and I'm the Designated Federal Officer for today's meeting. I will now invite our FDA participants to introduce themselves when called upon and to turn on their cameras for introductions. We will start with Dr. Dionna Green.

Dr. Green: Hi. Good morning everyone. My name is Dionna Green, and I am the director of the FDA Office of Pediatric Therapeutics.

Shivana Srivastava: Dr. Mohamed Mohamoud.

Dr. Mohamoud: Good morning everybody. My name is Mohamed Mohamoud. I'm a senior clinical analyst in the Office of Pediatric Therapeutics.

Shivana Srivastava: Dr. Ivone Kim.

Dr. Kim: Good morning. My name is Ivone Kim. I'm a senior medical officer in CDER's Office of Surveillance and Epidemiology.

Shivana Srivastava: Dr. Vasum Peiris.

Dr. Peiris: Good morning everyone. Vasum Peiris. I serve as the chief medical officer and director for Pediatrics and Special Populations at CDRH, our Center for Devices and Radiological Health. My clinical background and boards are in pediatrics, pediatric cardiology and adult congenital cardiology. Thank you.

Shivana Srivastava: Dr. Craig Zinderman.

Dr. Zinderman: Good morning everyone. Craig Zinderman. I'm the associate director for Medical Policy in the Center for Biologics Office of Biostatistics and Pharmacovigilance.

Shivana Srivastava: Great. Thank you. Additional FDA participants in today's meeting will introduce themselves when speaking throughout the meeting. I will now read the Conflict of Interest Statement.

Conflict of Interest Statement

Shivana Srivastava: The Food and Drug Administration is convening today, September 18th, 2024, 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 meeting involving specific parties, products, devices, and biologics for which the Committee will discuss postmarket safety events reported for these products. With the exception of the industry representative, all standing members of the Committee are special

government employees or regular government employees from other agencies, and are subject to federal conflict of interest laws and regulations. The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found in 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 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. This may include interests that are current or under negotiation. No temporary voting members or regular government employees were added to the Committee for this meeting. Therefore, the conflicts-of-interest screening was limited to standing members of the PAC.

FDA has determined that 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 consumer representative, we would like to disclose that Ms. Randi Oster is participating as a voting representative, acting on behalf of consumers, not on behalf of any organization, company or product. With respect to the meeting's patient representative, we would like to disclose that Dr. Gianna McMillan is participating as a voting representative acting on behalf of patients, not on behalf of any organization, company, or product. The consumer and patient representatives are special government employees, and as such have been screened for conflicts of interest.

With respect to the meeting, Dr. Jennifer Goldman is participating in this meeting as a Pediatric Health Organization Representative, and that is a non-voting position. With respect to FDA's invited industry representative, we would like to disclose that Dr. Robert Nelson is participating in this meeting as a non-voting representative, acting on behalf of regulated industry. This representative is not a regular 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 a subsidiary with a product that is coming before the Committee. In accordance with our regulations at 21 C.F.R. 14.86 (c)(4), Dr. Nelson has been reminded that any 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.

To ensure transparency, we encourage all Standing Committee members to disclose any public statements that they have made concerning the products at issue. We would like to remind members that if the discussions involve any other firms or products not already on the agenda for which a PAC member has a personal or imputed financial interest, the participant will need to exclude themselves from such discussion and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial relationships that they may have regarding the topics that could be affected by the Committee's discussions. Thank you. I will now turn the meeting back to our chair.

Dr. Fischer: We will now proceed with the opening remarks from Dr. Dionna Green, the director of the Office of Pediatric Therapeutics.

FDA Opening Remarks

Dr. Green: Thank you, Dr. Fischer, and good morning, everyone. I would like to welcome our Committee members and guests who are joining us for today's Pediatric Advisory Committee meeting. I want to start by first thanking the Committee for the time that you have taken to review the advanced materials and prepare for today's meeting. Your perspectives and input on topics brought before the Committee are highly valuable to the agency. I would also like to thank the following groups. The FDA staff who performed or contributed to the pediatric-focused postmarket safety reviews that are the

subject of today's meeting. The FDA staff members who are participating today, and all those who contributed to the logistics and the planning for the Advisory Committee meeting. And our AV staff for their technical support. Last but not least, I would like to thank the members of the public who are joining us today. Next slide please.

At today's meeting, the Pediatric Advisory Committee is being convened 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. Before we proceed with the focus of today's meeting, I will first provide an update on the Pediatric Research Equity Act, also known as PREA, non-compliance letters, as required by legislation.

FDA issues PREA non-compliance letters to sponsors if they fail to submit within the required time frame a required pediatric assessment or report of a molecularly targeted pediatric cancer investigation, as appropriate. FDA has also issued such a letter if a sponsor failed to request approval for a pediatric formulation, as described in Section 505 (b) of the Food, Drug, and Cosmetic Act. Consistent with the act, FDA has also made publicly available on FDA's website the PREA non-compliance letter and sponsors response with certain redactions. If a sponsor has requested a deferral extension or submitted a waiver request by the due date of the pediatric assessment, or the report of the molecularly targeted pediatric cancer investigation, FDA has not issued a PREA non-compliance letter, unless FDA subsequently denied the deferral extension or waiver request. Next slide.

Since the last reporting on the non-compliance letters at the September 2023 Pediatric Advisory Committee meeting, there have been no new letters issued by CBER, the Center for Biologics Evaluation and Research, and there have been 24 new letters issued by CDER, the Center for Drug Evaluation and Research. Next slide. The information related to these letters are listed on this slide and the following slide, and can also be found on FDA's website. Next slide. Next slide. Now, in terms of the agenda for today's meeting, the meeting will proceed as follows.

We will first have a background presentation by the FDA. The open public hearing portion of the meeting will start at 11 a.m. Eastern and will end at 12 p.m. There will be a listing of the products evaluated in the pediatric-focused postmarket safety reviews completed by CDER.

This will be followed by a lunch break, which is scheduled at approximately 12:45 p.m. Next slide. The meeting will resume at 1:30 p.m. for Committee discussion of the CDER products and votes. This will then be followed by a listing of the CDRH products, with a subsequent discussion and vote, and the listing of the CBER products, with the subsequent discussion and vote.

There is time allotted for clarifying questions from the Committee at specified times during the meeting. We are scheduled to adjourn the meeting at approximately 4:00 p.m. Please note, however, that depending on the pace by which the meeting proceeds, it is possible that these times may shift. Next slide.

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

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

During the vote, all meeting participants aside from the Pediatric Advisory Committee will be moved to a breakout room. Meeting attendees trying to join the meeting during the time voting or vote tabulation is occurring will be placed in a waiting room until the meeting resumes. Once the meeting resumes, the voting results will be displayed and read into the record by the Designated Federal

Officer. Following which, each voting member of the Pediatric Advisory Committee will be called upon to state their individual vote for the record. Next slide.

Thank you for your attention, and I will now turn the meeting back over to our chairperson, Dr. Fischer.

Dr. Fischer: Thank you, Dr. Green, for that great presentation. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants to advise the Committee of any financial relationships they may have with the firms at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with the FDA's background presentation by Dr. Mohamed Mohamoud from the Office of Pediatric Therapeutics. You'll have the opportunity to ask clarifying questions at designated times in the meeting. Dr. Mohamoud, the floor is yours.

FDA Background Presentation - Pediatric-Focused Postmarket Safety Reviews for the Pediatric Advisory Committee

Dr. Mohamoud: Good morning everybody. The focus of my presentation today will give you a brief overview of the pediatric-focused safety review process from past to present. As you're aware, the review of pediatric-focused post-marketing safety reviews is a core duty of the Pediatric Advisory Committee. Next slide.

Specifically, my objectives will be to outline legislation that created the Pediatric Advisory Committee, or PAC, and established the PAC's role in the post-marketing pediatric safety monitoring; summarize past and ongoing efforts to optimize how the PAC reviews pediatric-focused post-marketing safety reviews; and present new changes for future engagement in post-marketing pediatric safety monitoring. Next slide.

The Best Pharmaceuticals for Children Act of 2002, or BPCA, followed the Food and Drug Administration Modernization and Accountability Act of 1997, or FDAMA, and was the first legislation that established the concept and the rules for what is called pediatric exclusivity. This legislation provided incentives and FDA authority to encourage the study of drug products in pediatric patients, but was scheduled to sunset in 2002 when BPCA was passed. BPCA established the Voluntary Incentive Program, through which a sponsor may gain market exclusivity for six months if they performed pediatric studies as specified in the written request issued from FDA. This applies to drugs in development as well as products that are already marketed. FDA may request a pediatric study to evaluate the same indication intended or approved for adults, but it also may request that a sponsor conduct a pediatric study for a different indication, including one not approved for adults. This is a key feature that distinguishes BPCA from the Pediatric Research Equity Act, or PREA, which I will go over in the next slide.

This Act also established the Office of Pediatric Therapeutics within the Office of the Commissioner. This Office coordinates and supports all activities within FDA involving pediatrics. BPCA also created a role for the National Institute of Health in supporting pediatric drug studies for off-patent drugs. For drugs that are off patent, BPCA directed NIH to create a list of pediatric therapeutic priorities and to propose written requests for studies to FDA. As a partial response to concerns about long-term safety, and to address the difficulty in identifying pediatric-specific safety signals, as they are often submerged in a larger number of reports submitted for adults, Congress required as part of the BPCA, the evaluation of safety in pediatric-focused post-marketing safety reviews one year following the date on which a drug receives pediatric market exclusivity. Any report of an adverse event must be reviewed by the FDA Pediatric Advisory Committee, which at the time was a Subcommittee of the Anti-Infective Drug Advisory Committee. Next slide, please.

The Pediatric Research Equity Act, passed in 2003, followed the 1998 Pediatric Rule. The objective of this rule was to increase the labeling information relevant to pediatric use by requiring manufacturers to provide data and information for products when the disease or the condition is similar in adults and children, and if either widespread use is anticipated or the product is a therapeutic advance in pediatrics. The Pediatric Rule was eventually invalidated and was deemed to have exceeded the

FDA's authority, and thus PREA or the Pediatric Research Equity Act, was passed by Congress in 2003, which included many provisions of the Pediatric Rule. PREA also required sponsors of drugs and biologics to include an assessment of safety and effectiveness for the indication claimed in all relevant pediatric subpopulations.

PREA applies to any marketing application involving a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration. In addition, PREA required sponsors to develop an appropriate formulation for each pediatric age group for which an assessment is required, as well as providing data to support dosing and administration. PREA also created the publicly deliberating Pediatric Advisory Committee in 2004 as a standalone committee, which until then, as I mentioned earlier, was a Subcommittee of the Anti-Infective Drug Advisory Committee. Next slide, please.

The Food and Drug Administration Act, or FDAAA, became a law in 2007 and renewed with modification BPCA and PREA, and introduced the Pediatric Medical Device and Improvement Act, which I will discuss in the next slide. It also extended the Pediatric Advisory Committee until 2012, and one of the modifications introduced by FDAAA is that it required sponsors, regardless of whether the study is pursuant to PREA or BPCA, demonstrated that a drug or a biologic is safe and effective, or whether the results of such studies within the pediatric population are inconclusive, the sponsor must submit labeling to include information about the result of these studies. FDAAA also strengthened FDA's authority to require sponsors to conduct post-marketing studies, including studies to assess a known serious risk related to the use of the drug, or a signal of serious risk related to the use of the drug when available data indicate the potential for a serious risk. This provided FDA another strategy for postmarket safety monitoring. FDAAA also continued the requirement for pediatric-focused post-marketing safety reviews, and expanded the products eligible for these post-marketing safety reviews to products regulated by CBER, including biologics and vaccine. FDAAA also changed the requirement for pediatric-focused post-marketing safety reviews from one year following the date on which a pediatric drug receives market exclusivity to follow any pediatric labeling change pursuant to BPCA and PREA. Next slide, please.

The Pediatric Medical Safety Improvement Act, which is part of FDAAA 2007, is the legislation that required pediatric-focused post-marketing safety reviews for pediatric medical devices approved through the Humanitarian Device Exemption Program, or HDE process, when a sponsor requests a profit-making waiver and FDA approves that waiver. The pediatric population is defined by the Center of Devices and Radiological Health to be 21 years of age and younger. Humanitarian Device Exemption, or HDE, is a medical device intended to benefit patients in treatment or a diagnosis of a disease or a condition that affects or is manifested in not more than 8000 individuals per year in the United States.

For HDEs, the PAC is tasked with the annual review of HDEs with humanitarian use designation, and a device designation criteria for profit making in pediatrics, as well as adverse events to detect any new safety concerns. Because this is an annual review, you may see the same devices come up for review yearly. Additionally, new HDE devices are added to the review cycle as they get approved. Next slide, please.

The Food and Drug Administration Safety and Innovation Act of 2012 reauthorized BPCA and PREA permanently, and also extended the Pediatric Advisory Committee permanently. FDASIA also continued the requirements for the PAC to review adverse events in the pediatric population by requiring FDA's ongoing pediatric-focused post-marketing safety reviews to be initiated 18 months after the pediatric labeling change, instead of the previous one-year period. Next slide, please.

For all pediatric-focused safety post-marketing reviews, the focus of the analysis is on adverse event reports obtained from passive surveillance sources using spontaneous reporting databases, such as the FDA Adverse Event Reporting Database for drugs and therapeutic biologics, the Vaccine Adverse Event Reporting System for vaccines, or VAERS, and the Manufacturer and User Facility, device experience database, or MAUDE, for devices. All these spontaneous reporting databases contain information on adverse events and medication or vaccine errors, or device malfunction reports submitted to the FDA from healthcare professionals, consumers, and manufacturers. The databases are designed to support FDA's post-marketing safety surveillance programs for drugs, biologics, vaccines, and devices. These surveillance systems are subject to many limitations, including underreporting, valuable report quality and accuracy, missing or incomplete information, inadequate data regarding the

number of doses administered, and unverified medical information. In addition, the incidence and the prevalence of an adverse event cannot be determined from these surveillance systems alone due to the potential for underreporting of events and the lack of information about the frequency of medical product use. Other sources of safety data presented in these reviews include the status of post-marketing studies, the manufacturers postmarket periodic safety reports which summarize the adverse events reported to the sponsors, and a search of the peer-reviewed articles pertaining to safety to capture anything not reported to the agency or the sponsor. Next slide, please.

The graph below shows the number of labeling changes for the pediatric population under certain federal laws, including PREA and BPCA. The number of pediatric labeling changes have been increasing since the passage of FDAAA in 2007, which in turn increases the number of products eligible for a pediatric post-marketing safety review. The number of pediatric labeling changes includes each individual labeling change approved by the FDA. One product may undergo several pediatric labeling changes. For example, a product labeling may be updated once studies in older children have been reviewed by FDA and again years later after studies in younger children have been completed. Next slide, please.

With the start of pediatric-focused post-marketing safety review processes, all reviews were presented to the PAC at an Advisory Committee meeting. With the increasing number of products eligible for these reviews, the Office of Pediatric Therapeutics introduced different approaches for how FDA presents the reviews to the PAC, with the goal of optimizing use of FDA and PAC resources. For example, abbreviated reviews were introduced in 2006 and were reserved for products with no identified new safety concerns and were adequately labeled for pediatric patients. After different iterations of abbreviated reviews, including justified abbreviated reviews and designated abbreviated reviews in 2010 and 2012 respectively, we introduced in 2016 our current process of web posting reviews for products that are designated as low safety risk. This process started in 2016 for CDER products, and it was expanded to CBER in 2017, and CDRH in 2018. Next slide, please.

The web posting process starts with the respective center staff preparing the pediatric-focused post-marketing safety reviews. These reviews are then reviewed by staff from the centers and the Office of Pediatric Therapeutics. Based on the data presented in these reviews, a determination is

made if the products reviewed meet the designation of a low safety risk. This does not mean that these products are benign, but rather suggests that based on the information analyzed from post-marketing data sources at this time, that the safety profile of the product is consistent with current prescribing information. Thereafter, the products deemed low safety risk are shared with the PAC members for independent asynchronous review after a conflict-of-interest screening is completed. Products deemed low safety risk are also posted publicly on the FDA website for review. For products not deemed as a low safety risk, with safety concerns, for which a safety concern is identified in the review, these products are dropped from this process and will be presented at a future PAC meeting. Please note that products with multiple pediatric labeling changes may undergo this process multiple times, and the process is also reinitiated for new products 18 months after an approval of a pediatric labeling change. Next slide, please.

This graph shows the number of reviews presented to the PAC at a meeting over 18 years, from 2003 to 2021. From 2003 to 2021, a total of 398 reviews were presented to the PAC at a meeting. The first presentation to the PAC was by CDER in 2003. The first product presented by CBER was in 2010. Furthermore, the first product presented by CDRH was in 2011. You may notice that the number of reviews presented to the PAC at a meeting went down starting in 2016. This corresponds to the initiation of the web posting process that I just described. More products were being presented to the PAC via web posting to accommodate the presentation of products with safety concerns to the PAC. Additionally, the increasing number of products being web posted was also a result of the increasing number of pediatric labeling changes making more products eligible for a pediatric-focused post-marketing safety review. Next slide, please.

The criteria for determining whether a review will be web-posted was adopted from previous approaches used to streamline pediatric-focused safety reviews, like the abbreviated review process. The web posting of a review helped to decrease some of the backlog of CDER products awaiting reviews. Additionally, it led to more reviews being completed in a shorter duration of time and provided the PAC with more time to discuss products with safety concerns. For example, from 2016 to 2023, 364 pediatric-focused post-marketing safety reviews were completed by CDER, CBER and

CDRH. By contrast, as shown in the previous slide, 398 reviews were presented to the PAC between 2003 and 2021. Next slide, please.

Pediatric-focused post-marketing safety reviews for low safety risk products will continue to be sent to the PAC in advance of the PAC meeting for asynchronous review, as was previously done. The PAC members review will occur independently after a conflict-of-interest screening is completed to assess eligibility to review the product undergoing a review in this cycle. This means that PAC members may receive different packages of documents based on their eligibility to review certain products. The following are the changes we anticipate for products designated as low safety risk.

PAC members are encouraged to submit questions in advance of the PAC meeting via email, as some of you have done for this meeting. PAC members will discuss product designated as low safety risk at a PAC meeting to provide a public forum for discussion, as well as discussing these reviews in this meeting. During PAC meetings, PAC members can ask additional clarifying questions not submitted via email, and PAC members will then vote if they concur with FDA's recommendation of continuing routine, ongoing postmarket safety monitoring. Next slide, please.

So, what does ongoing routine post-marketing safety monitoring mean? It means that the product will return to ongoing surveillance that FDA does on a regular basis to detect possible safety concerns. This includes review and analysis of any safety concerns identified from spontaneous reporting databases, post-marketing clinical trials, observational studies, pharmacokinetic studies, as well as the peer-reviewed medical literature. FDA safety evaluators also review and assess and analyze incoming safety reports that FDA receives from sponsors, consumers, and healthcare providers. FDA also reviews the annual periodic safety reports from sponsors, and these reviews of adverse events include all population and are not specifically focusing on the pediatric population. So, when you're voting "Yes" on continuing routine, ongoing post-marketing safety monitoring, you are voting for all these measures to be part of the routine ongoing safety monitoring. Next slide, please.

In conclusion, we will continue to engage the PAC in low safety risk drug device and biological product safety reviews during PAC meetings to provide an open forum for discussion and obtain any recommendation the PAC may have. We will also continue to present reviews with new safety concerns to the PAC for discussion, and to obtain advice and recommendation from the PAC. We

will continue to engage the PAC in other Advisory Committee activities, including other topics outside the pediatric safety review process. And finally, we will explore alternative ways to optimize FDA's approach to conducting pediatric-focused post-marketing safety reviews to put FDA's and PAC resources to best use. Next slide.

This concludes the FDA background presentation. Thank you for your attention, and I welcome any clarifying questions you may have. Thank you.

Dr. Fischer: Dr. Mohamoud, thank you for your presentation. At this time, I'd like to ask the PAC members if there are any clarifying questions for either Dr. Green or Dr. Mohamoud. If you have a question, please raise your hand on the Zoom format and when called upon, please remember to begin by stating your name for the record. Miss Randi Oster, you can go ahead.

Clarifying Questions

Randi Oster: Yes. Hello. My clarifying question has to do with what the goal is, which is to optimize how PAC does reviews, and the understanding that it is based on the information available at times. I'd like to get an understanding-- As you look at the number of reports that are coming in, how do you evaluate if people even understand how to submit the report? Because the reports are limited in number, each one is critical. And I'd like to get an understanding when you're talking about explore alternative ways to optimize where you see the gaps currently and what you are looking to optimize in the future.

Dr. Fischer: Dr. Mohamoud or Dr. Green, any comments?

Dr. Mohamoud: Good morning. Thank you for the question. I think my goal when mentioning-- This is Dr. Mohamed Mohamoud, from the Office of Pediatric Therapeutics. The goal of mentioning optimizing FDA and PAC resources-- As you are aware, we sent you a bunch of documents to review. And that was sort of a lot of reviews, I think, to review at a certain-- Particular instance. So, we were thinking that we would come up with alternative ways where we can have perhaps, maybe more frequent meetings [Indiscernible – 00:52:10] that are being sent to you. And that way we optimize the process. Does that answer your question?

Randi Oster: So, just as consumer representative, I just would like to include optimizing-- Including the definition of optimizing, the number of reports that consumers make-- Send in, and their awareness

of the responsibility to submit adverse events. So, I'd just like to put that on the table for the FDA to consider.

Dr. Mohamoud: Thank you.

Randi Oster: Thank you.

Dr. Fischer: Any other clarifying questions for Dr. Mohamoud or Dr. Green? Oh, Dr. McMillan, go ahead.

Dr. McMillan: Thank you. This is Dr. McMillan. So, I just have a question about-- Looking at the reviews or the documents that we were sent to review. In many instances, there are serious events that are listed, or even death numbers, that say these instances are unassessable due to lack of information. So, I'm wondering how we're supposed to accept these unassessable instances. I know the FDA is doing their work behind the scenes, and if they've determined that that's not important, then fine. But I'm wondering if there's some kind of a nuance that I'm missing here in this kind of evaluation.

Dr. Mohamoud: Hello. Yes. Mohamed Mohamoud, Office of Pediatric Therapeutics. Thank you for your question. Yes. I think as I mentioned in the presentation, a lot of the data that's analyzed in these reviews is coming from spontaneous reporting databases. And one of the limitations of these databases is that there is sometimes incomplete information and missing information in these reports. The FDA, when there's a concern about a report, reaches out to sponsors to see if they have additional information or maybe can get additional information that they can share with the FDA. So, I assure you, that's also being done. And I also want to remind you and the Committee that this is not only way. The spontaneous reporting databases are not the only source of safety information, it's just one source that's put in context with other data sources, such as, you know, clinical trial information as well as, you know, animal studies, PK studies, observational studies to evaluate safety. So, before a decision is made about whether a safety concern is identified, the information from a variety of data sources is put into context, and then a decision is made on whether the safety issue is of concern or if that particular report is a concern.

Dr. McMillan: Okay. Thank you.

Dr. Fischer: Thanks for those great questions. Any other comments or questions for our speakers? Okay. If not, thank you to both of you. At this time, we will open the open public hearing session.

Open Public Hearing

Dr. Fischer: Welcome to the Open Public Hearing. If you wish to speak, please state your name and your affiliation, if relevant to this meeting.

The FDA 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, its direct competitors. For example, this financial information may include a company's or group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting, or grant money that your organization receives from the sponsor or a competitor.

Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships, to which you may state for the record. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this Committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this Committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing meeting to be conducted in a fair and open way, where every participant is listened to carefully, treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chairperson. Thank you for your cooperation.

We do not have any planned speakers, so if there is anyone who would like to speak at this point, please raise your hand on the Zoom platform.

Okay. I do not see any raised hands. So, at this time, if any member of the public wishes to speak, you can go ahead and email PAC@fda.hhs.gov. The open public hearing will remain open until noon.

We will continue with today's meeting agenda, unless a member of the public wishes to speak during this allotted time. We will now transition to the discussion about pediatric-focused postmarket safety reviews completed by the Center for Drug Evaluation and Research, represented by Dr. Ivone Kim. Go ahead, Dr. Kim. Thank you.

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

Dr. Kim: Thank you, Dr. Fischer. For the record again, 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 will now read the list of CDER regulated products that are under discussion at today's meeting. Please note I will be stating the trade names only. However, both trade and generic names will be listed on the following slides.

Please note also that in some instances, more than one product was included in the same review, and products that were reviewed together are listed together in these slides, and they will be voted on together at the conclusion of the Committee's discussion. I'll now begin stating the products into the record. Azstarys, Cafcit, Chantix, Cimduo, Temixys, Cleocin hydrochloride, Cleocin phosphate, Cleocin phosphate in dextrose 5% in plastic container, Clindamycin phosphate in 0.9% sodium chloride, Dyanavel XR. Next slide, please. Evekeo, Gattex, Gilenya, Tascenso, Januvia, Janumet, Janumet XR, Kapspargo sprinkle, Lithium, Lotemax, Lumason, Mavyret, Mircera. Next slide, please. Multrys, Tralement, Zinc sulfate, Selenious acid, Mydayis, Natroba, Pradaxa, Qelbree, Riomet ER, Teflaro, Tirosint-SOL, Tybost. Next slide, please. Ultravate, Lexette, Veklury, Vyvanse, Xaciato, Xeglyze, Xelstrym, and Yervoy. Thank you.

I will now transition the meeting back to Dr. Fischer, PAC Chairperson.

Dr. Fischer: Thank you. Thanks to all of our FDA speakers. We will now proceed with clarifying questions from the PAC. I will remind you to use the "Raise hand" button so that I'll know when to call on you. When called upon, just remember to state your name for the record before asking your question. Please go ahead and raise your hands on the Zoom function. Miss Oster, go ahead.

Clarifying Questions

Randi Oster: Yes. Yes. I want to talk about-- Well, first I want to say I've submitted a 23-page report to the FDA, going drug by drug, identifying the issues I had. I'm going for clarifying questions to talk about the four main issues that I saw with the drugs. And I would like a response to those four main issues. I can use a specific drug to identify where those issues are.

But the first issue that I'd like clarified is the issue of missing age. That should be pretty obvious, right? To ask the doctor or the parent how old the person is, and that becomes one of the reasons that the data that is coming in from these FAERS reports are eliminated. Just for some perspective. The number of reports is so few that each one is critical. In my background in aerospace, to keep the planes flying, we would allow for 3.4 defects per million occurrences. If you have five reports coming in that you're discounting for age, oh, my goodness. That's a lot of data that we're giving up on. So, the first issue is age. I'd like clarification.

The second issue I'd like to understand is the death rates of adults. Dr. Mohamoud talked about the fact that we look at the end point for adults for approving the drugs for children if the end point is the same. I would like to understand how death is used for saying that the drug is safe. I'll give one quick example. In the drug Kapspargo there were 205 reports that were excluded. There were 110 deaths, but in the adult population there were 6584 deaths. So, I would like to understand how we use the death rate for adults in our evaluation for children, especially if we're eliminating some of those reports in and on themselves.

And then my last two points that I would like clarification on is labeled adverse event. The data is not counted if it's previously included. My question is, at what point, if we are getting reports, do we start to say they're not happy with the drugs. Because there they're saying, "I'm having an adverse event." So, there's a communication issue. In some cases, it was 2%. But in some cases, we had 50% of the reports coming in for what you were-- We were eliminating because it was already on the label. There has to be some kind of a bar, where-- If that's what it's coming in for, we need to evaluate that. And then the last issue I'd like clarification on is unassessable reports; missing information. The data is eliminated for comorbidities, and if things are unknown, and-- How are we capturing that? In other words, if we're starting to see a pattern of the same drugs and the same problems, we can't just say,

"Well, it was because of something else. So, we've eliminated the report." We have to find what are the best practices and what is the information sharing.

So, those are my four issues. Age, adult death rates, labeled adverse event, and unassessable reports. How do we take that data and make sure we're using it to help make sure we are providing safe and effective medications? Thank you.

Dr. Kim: Thank you. This is Ivone Kim with CDER again. Thanks for all your questions, Randi. Miss Oster. I'll try to address some of the best of my abilities. So, to address the missing, miscoded age issue. So, for clarification, rarely reports that are submitted into FDA are coded with the wrong age. So, in the course of our evaluations for the PAC, we sometimes identify these reports. They're describing adult patients that are erroneously coded with pediatric ages. And when this occurs, CDER reviewers can ask the FAERS team to correct the miscoded age in FAERS for future evaluations, but the category of miscoded age in these pediatric reviews can also include reports where the date of birth or age is incorrectly reported. So, from the reporting end. Reporting on many data fields when you're submitting data to FAERS is totally voluntary, and FDA just encourages-- Still encourages the submission of these adverse events, even if not all the data fields are known. So, whether a report is determined to be pediatric or adult for the purposes of our reviews, the post-marketing pharmacovigilance reviews of pediatrics for the PAC really depends on how they're coded. And we only exclude patients from our review if they're erroneously identified an adult patient as a pediatric patient. So, I hope that's answered the question.

Randi Oster: Thank you.

Dr. Kim: Yeah. The next question. Forgive me. If you could remind me what your second question was.

Randi Oster: How do we incorporate adult death rates into the evaluation? Especially if the numbers for the children are smaller, but we're seeing high adult death rates.

Dr. Kim: Right. So, the focus of these pediatric pharmacovigilance reviews is on the pediatric FAERS reports. We do not review the adult- the adult reports from these reviews.

Also, I want to mention that we don't extrapolate adult data into pediatric data for post-marketing pharmacovigilance. That said, with routine pharmacovigilance practices and activities, we do review

adverse event reports from all populations, including adults and pediatrics. So, we're not necessarily missing that data. We're just not focusing on those for these pediatric reviews for the PAC. And did you have-- I wanted to clarify make sure that you had no--

Randi Oster: No. I'm just-- I'll just leave that for my peers on the committee to think about and to-- If they have additional questions. I have my-- I understand the point of view. I'll let other people absorb it and then comment on if they-- why they think that's a good idea or not a good idea.

The next one was labeled adverse event, and at what point do we start to see the percentages rise that they're already submitting the reports for something that you're saying was on the label so we then discount it. At what point do we start to relook at the label and say, maybe these adverse events that are coming in we need to think about.

Dr. Kim: Ivone Kim, again, with CDER. Thank you for that clarification. So, first, I think it's important to recognize that because this is a spontaneous event reporting system and it's voluntary, we don't receive reports for every adverse event or medication error that occurs in the product, and many factors can influence whether an event can be reported. So, there are factors such as the product's length of time in the market or whether there's been some publicity related to the product. Therefore, the information that we get in these reports cannot be used to estimate the incident rates for the reactions that are reported to us. So, when we're talking about calculating rates that are increasing for labeled events or otherwise, we just cannot calculate the rates from these data.

The other point is on labeled adverse events. So, the focus again is on the reviews is to identify serious unlabeled or unknown adverse events. And when the reviews that-- When we do the review, the reports describing known or adverse events, we look for evidence of new features of these adverse events. Right? We look at increased severity or specificity for an adverse event to see if this represents something new that warrants a change in labeling. CDER follows the manual of policies and procedures for newly identified safety signals. We call it the NISS MAPP. And we use this to determine if any new features of a labeled event represent a new safety signal. We also have guidances for industry that describe considerations for whether an adverse event should be labeled and if so, in what section of the label. We follow these same guidances when we determine whether there's a potential new signal that comes from- that warrants new labeling or a change in labeling.

So, as an example, if we find that there's a product that has a labeled adverse event for elevated liver enzymes in the adverse reaction section of the labeling, but we keep identifying cases where liver failure or a more serious liver injury, we will perform a causality assessment and evaluate these cases of liver failure to determine whether labeling or other regulatory actions are warranted. Thank you.

Randi Oster: And then the last one was the unassessable reports where there's just missing information. And my question really wants to understand how are you collecting the data to see commonality between these co-morbidities, so that there could be some best practices for other pediatric patients when you find similarities instead of just eliminating the data.

Dr. Kim: Ivone Kim, CDER again. Thank you for that question. So, first, I wanted to go back and touch on the sort of missing data and kind of unassessable reports. The voluntary nature of reporting inherently leads to variation in data quality and completeness across FAERS reports. So, FDA has implemented changes that are aimed at improving data in FAERS, and we do so in the form of form modifications, including the development of form, specifically for consumers in plain language. And we've also engaged in educational outreach, and we developed training materials like MedWatch Learn, which is available online. And this teaches healthcare providers, patients and other caregivers how to give the complete form-- On how to complete the form and how to report problems to FDA. So, you know, when we're talking about unassessable cases, we're really talking about causality assessments. Unassessable reports are eliminated from being included when we cannot tie the adverse event to the reported product.

There are only a few criteria for submitting adverse event reports to FAERS. First, the report has to identify a product, it has to identify a patient, an adverse event and a reporter. But again, due to the nature of this spontaneous reporting, the level of data or detail in each report can be variable, and the reports are missing important information oftentimes. So, we perform a causality assessment between drug events and for each case that we come across in these pediatric reviews for the PAC. Again, using elements from the guidance for industry for good pharmacovigilance practice. And we use adapted elements from the World Health Organization causality categories. We consider a report to be unassessable for causality if we don't have sufficient information reported. And information can be

things like unknown time to event, unknown presence of concomitant medications or comorbidities, or unknown clinical course or outcome. And there can also be unassessable for causality if they contain contradictory or inconsistent information.

Dr. Fischer: Ms. Oster, any other follow up questions?

Randi Oster: I'll let- I'll let the rest of the PAC members absorb that and just know that in my report I did go drug by drug, and in some cases the numbers are very high in terms of-- And so I won't go through each one, but that has been submitted to the FDA. And if they can go through each drug and respond to that, that would be helpful. But we do not have to do that today.

Dr. Fischer: Thank you, Ms. Oster. We will likely have time to circle back to you if you have other follow up questions regarding those specific topics or anything else.

Dr. Kim, while I have you, I have a couple of questions myself for you. This is Gwen Fischer. One is a lot of these drugs are being used globally, and I'm wondering if you have either an informal or formal process with the other regulatory institutions to share flags that come up across different nationalities. Thank you.

Dr. Kim: Ivone Kim, CDER. Thank you, Dr. Fischer, for that question. Yes. FDA meets regularly with other, foreign regulators to discuss potential safety signals or regulatory changes.

Dr. Fischer: Thank you. This is Gwen Fischer with my second question. I'm wondering if there are ways for all three agencies really to educate and encourage providers to submit adverse events when they occur and to remind them that that is something that we should all be doing. You're on mute, Dr. Kim. You're still on mute.

Dr. Kim: Can you hear me now?

Dr. Fischer: There we go. Yeah.

Dr. Kim: There you go. Ivone Kim, CDER. Thank you for that question as well. So, as I mentioned, we do engage in some educational outreach, office space, but also for global training materials like MedWatch Learn. But-- So, when you-- And I wanted to clarify, when you say the different agencies, you mean the different centers? Or--

Dr. Fischer: No. CBER, CDRH, and CDER. Yes. The three agencies.

Dr. Kim: Yes. So, I can only speak for CDER, but I believe they're training materials from FDA in general. But for, the CDER educational trainings there are several programs that we let out. There is some outreach that we perform within the Office of Surveillance and Epidemiology for training programs to teach health care providers how to- how to report to FDA MedWatch.

And I wanted to clarify as well that consumers and health care providers can also report adverse events or suspected events to the products, manufacturers and applicants. And these manufacturers are required to submit those reports to FDA as well, by regulations.

Dr. Fischer: Thank you, Doctor Kim. Just a reminder that the public hearing is still open. If you would like to comment, you can comment now live. Or you can also email the FDA if you'd like to comment. Looking for any hands up from either open public hearing or PAC members who'd like to ask any clarifying questions. Just a reminder also, that now is an appropriate time to be asking clarifying questions about the individual products that Dr. Kim presented. Dr. Holubkov, go ahead.

Dr. Holubkov: Hi Rich Holubkov. I just wanted to- I just wanted to commend you on this process. I mean, I know you guys are going through lots of databases, lots of events. As a statistician, it's quite impressive. A very detailed, probably a naive question. As you said, specific things like caffeine citrate, the Cafcit. This was one- This was one where I didn't see in too many other things where many of them- - I realize this is an injection of a CNS stimulant as a treatment. And over a third of them, you did the FAERS search and then, about a third of them-- Finally, you said you search for injection, but then 14 of the- 14 of the 43 events did not describe injection. I was wondering, what is-- Is it something unique about that product that would be that would cause it to be misstated? Maybe because of the way of administration or something like that. Yeah, thanks. Thanks for the clarification.

Dr. Kim: Ivone Kim, CDER, again. Thank you for that question, Dr. Holubkov. So, nothing unique about this product. I think a lot of the times when we have-- It is an issue of coding sometimes. Sometimes reports describe a historical use of caffeine citrate, very remote from the actual adverse event that is reported. That's when we do the case level evaluation and we determine that caffeine citrate was not actually involved. And sometimes there is just a miscoding. Although they link this report- a particular report with caffeine citrate, it might actually be reflecting another caffeine product.

Dr. Holubkov: Since I have you on the line, just another general question. Perhaps this is something probably very similar to what Ms. Oster asked- Dr. Oster asked earlier. Many of these- many times you eliminate in commonly used product due to concomitant medical conditions. Is that decision made-- How is that- How is that decision made that an event kind of fades from concern or a new safety signal because of a concomitant condition. Is that done kind of verbatim based on a list of conditions for a particular- for each particular product? Or is it kind of case by case? Just wondering about that process. Thank you.

Dr. Kim: Ivone Kim. CDER. Thank you for that question again. This is where the case level evaluation for all the reports that we identify for the PAC reviews come into play.

We categorize some reports as adverse event more likely due to concomitant medications or comorbidity. When we do these case level analyses and we use-- All the safety evaluators have clinical background. So, when we use our expertise and we do the causality assessment, we know that- we might know in some cases that the adverse event is more proximately or more definitely related to another product or condition.

So as an example, we may have reports describing a patient taking a certain drug who is also receiving chemotherapy, and the report may describe hair loss. Depending on the clinical context, the hair loss could be more likely related to the chemotherapy rather than the drug of interest, and we really rely on the clinical context, our clinical background and expertise, and our knowledge about the drugs reported drugs pharmacology.

Dr. Holubkov: Thank you.

Dr. Fischer: Dr. Kim, this is Gwen Fischer. Just asking a follow up question from Dr. Holubkov. Regarding a medication like caffeine citrate or other drugs that have been used for traditionally a long time in pediatrics. I'm curious, the manufacturer may change, the site of manufacturing may change. Is there a way that the FDA notes those time periods for potential adverse events that may be related to that versus the drug itself?

Dr. Kim: Ivone Kim, CDER again. Thank you for that question, Dr. Fischer. So, we-- If we notice a pattern of events that are reported with a particular drug as we perform these pediatric safety reviews for the PAC, we may look at the history of a product and certain changes to provide context for this

potential safety signals. But we don't necessarily look for-- We don't have that information, honestly, coming through to the FAERS to analyze that specifically.

Dr. Fischer: Thank you. I was just thinking specifically about instances where disasters that occurred at manufacturing sites caused the closing of specific drug manufacturing sites, which led to a change in those manufacturing areas, which might change the quality of the drug or some of the preservatives that are used.

While I have you. I'll ask you one other question. So, you mentioned recording instances where safety events were thought to be related to drug interactions. Is there a way that you are cross-referencing those drug interactions for future information?

Dr. Kim: Ivone Kim, CDER. Thanks for that question. Great questions. Yes. So, when we review the adverse events that are reported through our review of the pediatric data, we look for potentially new signals and some of these can be drug-drug interactions. If we find sufficient evidence to indicate that we have a potential new signal, again, we follow the FDA's manuals of policies and procedures to evaluate newly identified safety signals, the NISS MAPP. But if we don't find sufficient evidence of a new signal through the NISS MAPP, we do kind of keep an eye on these potential signals, and we incorporate these in our regular surveillance of the drugs. All U.S. marketed drug products and biologics, including some other products, have constant monitoring as part of routine pharmacovigilance activities.

Dr. Fischer: Thank you. I appreciate that. I will stop holding up the floor and see if there are others who would like to speak. Just go ahead and raise your hand on the Zoom platform. Dr. Guillory, go ahead.

Dr. Guillory: Yes. Thank you. The question I had-- I know age was brought up and I know you look at all the adverse effects. In something like caffeine that may be used heavily in a neonatal population, do you really take that out and look at it in more detail because it's a special population?

Dr. Kim: Ivone Kim, CDER. Thank you for that question. I wanted to clarify. Are you asking if we look specifically at some age bands when we're performing reviews on certain drugs?

Dr. Guillory: Especially for caffeine. Yes.

Dr. Kim: Okay. Thank you. We do. We look at all pediatric age ranges for our reviews for the PAC. But in cases where we know that there are certain populations of interest or subpopulations, such as the

caffeine products, we do pay special attention to that age range. But, you know, sometimes it's important to look at patterns and age ranges where we don't expect to see use of caffeine. So, we are doing a hands-on sort of case level evaluation for all the reports. But we are taking into consideration the drug use in the real-life setting.

Dr. Fischer: Thank you. Any other questions from the PAC or also any folks who would like to speak now in the open public hearing, which is still open. Go ahead and raise your hands on the Zoom platform if so.

Okay. I don't see any hands. Thank you, Dr. Kim for those excellent answers. We will go ahead and proceed to the vote. So please change the slide-

Shivana Srivastava: -Hi Gwen. Oh, apologies.

Dr. Fischer: Go ahead.

Shivana Srivastava: This is Shivana. Actually, Ms. Oster and Dr. Jones have questions. We'll proceed forward with their questions, and then I'll make a comment afterwards.

Dr. Fischer: Oh, apologies. Dr. Jones, why don't you start?

Dr. Jones: Yes. I actually have a question about the voting procedure. If you have a conflict of interest since all the products are batched. You would recuse from the entire voting, is that correct?

Dr. Fischer: There will be an opportunity to vote individually on each item that was presented by Dr. Kim. They're all just batched into one form.

Dr. Jones: Okay. Thank you.

Dr. Fischer: And we can review that too when we get to voting. Ms. Oster, go ahead.

Randi Oster: That was-- I had a similar question. That there were certain drugs that I will say yes to, and certain ones that I will say no to. I'll have the opportunity to break them out on a drug-by-drug level?

Dr. Fischer: Yes. And we will go through the voting procedures here shortly.

Randi Oster: Thank you.

Dr. Fischer: Thank you for those questions. Shivana, any other hands up that I'm missing?

Shivana Srivastava: Not that I see at this time. And I just want to state publicly, for the record, we have no further comments from any of the public at this time. So, we will proceed forward with the agenda.

Dr. Fischer: Thank you. So, we will go ahead and close the open public meeting portion of this committee meeting and proceed to the vote. If we could move to that slide. Okay. Committee vote-

Shivana Srivastava: -Hi, Gwen. Apologies. The open public hearing will stay open until 12. We'll just continue with the meeting agenda and circle back at noon.

Dr. Fischer: Gotcha. Thank you. So just to reiterate, the open public meeting is still open and will close at noon Eastern time.

So, we'll proceed to the voting question. In the meantime, the voting question is being displayed on your screen. It states: FDA recommends continuing review ongoing, post-market safety monitoring of each of the CDER products under discussion. The question that the PAC is being asked to answer is, "Does the Pediatric Advisory Committee concur with this plan?" The options are yes, no, abstain or recused. Are there any questions regarding the wording of the question? Go ahead and raise your hand and state your name for the record if so. I don't see any hands.

We will now proceed with the question and open the question for further discussion. 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. Are there further clarifying questions on the voting question before us? Raise your hand if so. Ms. Oster, go ahead.

Randi Oster: All right. I just want to clarify, because I want to say yes to some and no. So, is this vote for all of them or for-- Are we going to get each drug?

Dr. Fischer: Shivana, would you like to clarify?

Shivana Srivastava: Hi, Randi. Yes. The vote will be per drug. Per product. Yes. So, that's-

Randi Oster: -So, we will see- We will see Azstarys. We'll see Cafcit. We'll see each one.

Dr. Fischer: Yes.

Shivana Srivastava: Correct. Yes.

Dr. Fischer: And you'll this will make more sense when you see the ballot.

Randi Oster: Okay.

Shivana Srivastava: And Dr. Jones, back to your original question. You will not be recused from the whole batch of products. It will just be for those particular products.

Dr. Jones: Okay. Thank you.

Dr. Fischer: Okay. If there's no further questions, we'll now begin the voting process. I would like to add, after votes are collected, PAC members will have the opportunity to summarize their votes into the record and state any reasoning beyond your-- Behind your vote. At this time, all voting members of the PAC, the Designated Federal Officer and AV staff will enter the voting room, and all other meeting attendees will join a breakout room. At the conclusion of voting, the meeting will resume and everyone will filter into the main meeting room. The vote will then be displayed on the screen, and the Designated Federal Officer will read the vote from the screen into the record.

I would like to add, although the meeting is not officially on a break while the committee is voting, you may step away during this time, but we strongly recommend to not exit the meeting. If you choose to exit, you will be placed in a waiting room until the meeting resumes. Thank you for your patience.

Okay. Thank you and welcome back, everyone. This is Gwenyth Fischer. First of all, do we have any more speakers for the open public hearing? Please, raise your hand on the Zoom platform if you do. Okay. I don't see any. So, without any further comments, I'd like to call the open public hearing to a close. Thank you.

We are now ready to see the results of the vote if they could be displayed, and I will turn the meeting over to the DFO.

Shivana 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 CDER products under discussion?" The results are: Azstarys, there were-- There are 11 yeses, zero noes, zero abstains, zero recusals. For Cafcit, there are ten yeses, one no, zero abstains, zero recusals. For Chantix, there are eight yeses, one no, zero abstains, and two recusals. For Cimduo and Temixys, there were eight yeses, one no, zero abstains, and two recusals. For Cleocin hydrochloride, Cleocin Phosphate, Cleocin Phosphate in dextrose 5% in plastic container, Clindamycin Phosphate in 0.9% sodium chloride, there are eight yeses, one no, zero abstains and two recusals. For Dyanavel XR, there are 11 yeses, zero noes, zero abstains and zero recusals. For Evekeo ODT, there are 11 yeses, zero noes, zero abstains and zero recusals. For Gattex,

there are ten yeses, one no, zero abstains, and zero recusals. For Gilenya and Tascenso, there are ten yeses, one no, zero abstains, and zero recusals. For Januvia, Janumet and Janumet XR, there are nine yeses, one no, zero abstains, and one recusal. For Kapspargo Sprinkle, there are ten yeses, one no, zero abstains, and zero recusals. For Lithium, there are ten yeses, one no, zero abstains, and zero recusals. For Lotemax, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Lumason, there are ten yeses, one no, zero abstains, and zero recusals. For Mavyret, there are ten yeses, one no, zero abstains, and zero recusals. For Mircera, there are ten yeses, one no, zero abstains, and zero recusals. For Multrys Tralement, zinc sulfate, selenious acid, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Mydayis, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Natroba, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Pradaxa, there are ten yeses, one no, zero abstains, and zero recusals. For Qelbree, there are ten yeses, one no, zero abstains, and zero recusals. For Riomet ER, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Teflaro, there are ten yeses, one no, zero abstain, and zero recusals. For Tirosint-SOL, there are ten yeses, one no, zero abstains, and zero recusals. For Tybost, there are ten yeses, one no, zero abstains, and zero recusals. For Ultravate and Lexette, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Veklury, there are ten yeses, one no, zero abstains, and zero recusals. For Vyvanse, there are ten yeses, one no, zero abstain, and zero recusals. For Xaciato, there are nine yeses, one no, zero abstains, and one recusal. For Xeglyze, there is 11 yeses, no noes-- I'm sorry, zero noes, zero abstains, and zero recusals. For Xelstrym, there are ten yeses, one no, zero abstains, and zero recusals. For Yervoy, there are ten yeses, one no, zero abstain, and zero recusals. Thank you.

Please refer to the meeting minutes to see the tabular summary of how individual PAC members voted for each product. (This statement was added to the transcript to provide additional information for the reader)

Dr. Fischer: Thank you. Now that voting for CDER has been completed, we will go down the meeting roster and have everyone who voted state their name, vote and if you want to, you can state the reason why you voted as you did into the record. I would suggest using the phrase: “I voted yes for all products except____.” and then explain your reason for voting no, if you did so. Also, if you see an error, please correct it for the record. We will start with David Callahan. Dr. Callahan, if you could-- There you go.

Dr. Callahan: I voted yes for all products except for the three products that were recusals.

Dr. Fischer: Thank you. Angela Czaja.

Dr. Czaja: I voted yes for all products.

Dr. Fischer: Thank you. Douglas Diekema.

Dr. Diekema: I voted yes for all products.

Dr. Fischer: Thank you. Charleta Guillory.

Dr. Guillory: I voted yes for all products.

Dr. Fischer: Thank you. Richard Holubkov.

Dr. Holubkov: I voted yes for all products, except the three for which I have a recusal conflict-of-interest.

Dr. Fischer: Thank you. Bridgette Jones.

Dr. Jones: I voted yes for all products except for the two I was recused from.

Dr. Fischer: Thank you. Steven Krug.

Dr. Krug: Hey, Steve Krug here. I voted yes for all products.

Dr. Fischer: Thank you. Gianna McMillan.

Dr. McMillan: I voted yes for all products. But note I'm uncomfortable with brief reports that include multiple instances of missing data or unexplainable serious events and deaths, but I'm confident in the FDA's ability to do detailed analysis of each of these instances when they're preparing the reports. And I think the reporting system is flawed, and perhaps the PAC might want to address this in the future.

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

Roberto Ortiz-Aguayo: I voted yes for all products.

Dr. Fischer: Thank you. Randi Oster.

Randi Oster: I voted-- Oh, that’s okay. I voted yes for nine products and no for the remaining. I will not go through each one. I will take one as an example. And the FDA has received all of my comments on the drugs, but for the purpose of the PAC, what I'd like to just do is just go through one that I voted no for, and that was Kapspargo. And in this case, there were nine- 205 reports that were excluded that included 110 deaths. Five of them were for age, which is 5.8%. The adult population had 6,584 deaths. We have discussed the fact that that is not part of the evaluation that is included in. Could this affect

children? And then for labeled adverse events, 17% of the reports were excluded. And 21 of the reports were of people that died. So, the issue is each one of these reports is critical. We have small data. And from a statistically significant perspective, just excluding that information is not telling. Okay.

So, we need more reports. I'm happy to hear about this MedWatch video. And I would like to challenge the FDA that in every single pharmacy there is a poster that says "If you have an adverse event, please report it" because we need more reports, and excluding these numbers is directionally not showing the data that I believe is out there. So, the FDA can go through each one of my noes and see the examples there. Thank you.

Dr. Fischer: Thank you. And to wrap up our CDER vote. Michael White.

Dr. White: Michael White. I voted yes for all of these, but I would like to comment that I was previously on the Pediatric Advisory Committee, and there is an ongoing concern for our lack of access to data that might be available, particularly within the electronic medical record system. And we just don't seem to be making a lot of progress at getting access to that. Thank you.

Dr. Fischer: Thank you for everyone's very thoughtful comments. We will now wrap up our CDER stage of this meeting and go to lunch. Lunch will conclude at 1:30 Eastern time. We ask that you just be back a couple minutes beforehand so we can get the Zoom set up. And at that point we will start our CDER-- CDRH part of this meeting. Thank you.

Shivana Srivastava: I would like to just remember- remind all panel members that there should be no communication of the meeting topics during the break or lunch, amongst yourselves or with any member of the audience. Thank you, Gwen.

Roberto Ortiz-Aguayo: Can you clarify? Was that 1 or 1:30?

Shivana Srivastava: 1:30.

Dr. Fischer: 1:30 will be our return time.

Roberto Ortiz-Aguayo: Thank you.

Dr. Fischer: Okay. Welcome back everyone. Our DFO just has a couple of general announcements and then we will get started again.

Shivana Srivastava: Welcome back everyone. Thank you, Gwen. I just wanted to verbally state for the record that all of our individual- that all of your individual votes are captured in the spreadsheets that

are displayed and will be fully captured in the meeting transcript. Thank you. I'll hand it back to you, Gwen. Thank you.

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

Dr. Fischer: Thanks, Shivana. We will now transition to the discussion about pediatric focused post-market safety reviews completed by the Center for Devices and Radiological Health, represented by doctor Vasum Peiris. You have the floor, Doctor Peiris.

Dr. Peiris: Thank you, Doctor Fischer. Next slide. Thank you. This section will cover these six listed humanitarian used devices and I'll read them off for the record. Contegra Pulmonary Valved Conduit is number one. Number two, Enterra Therapy System. Number three, Flourish Pediatric Esophageal Atresia Device. Number four, Pleximmune In-vitro Diagnostic Test. Number five, Pulserider Aneurysm Neck Reconstruction Device. Number six, Sonalleve MR-Hifu device. Dr. Fischer, handing it back to you.

Clarifying Questions

Dr. Fischer: All right. Thank you, Dr. Peiris. We will now proceed with any clarifying questions regarding CDRH in general or these specific devices. Go ahead and raise your hand on the Zoom platform if you'd like to speak. Ms. Oster, go ahead.

Randi Oster: So, okay. Hello? Yes.

Dr. Fischer: Yes, we can hear you.

Randi Oster: Okay. So, my question is on the Enterra. I just want to understand a little bit more about the electric shock that was received by some of the patients. And specifically, I want to understand, was this something that parents should have been trained to monitor the devices? You know, what is the level of ability? How- if so, you know, how are we communicating that? Because, 8% of the complaints were for shock. And I don't want us to think that 8% is a low number, right? You know, in terms of, errors that are acceptable for high performing systems that would be a very high number. So, I would like to understand a little bit more about the electron electric shock.

Dr. Peiris: Yeah. Thank you very much for the question. I think we've discussed earlier that there is certainly, aspects of our surveillance systems where we may not have the full denominator or numerator

in some of these situations, but your point in bringing up the 8% with respect to the reports that we have access to is correct and that is what was provided in the in our executive summary. And I agree with you. Certainly, we want to get to a point where there could potentially be no adverse events in any device used for any medical product use, but with any type of medical product devices included, there likely is going to be some level of risk and that trade off of benefit risk is what we consider when we're approving these devices.

To answer your question about whether there is training, this is part of the communication that generally takes place between the health care providers and the patients and their families to ensure that they understand what the issues that they should be aware of after a device like this is placed. And if there are certain levels of discomfort or shocks that are inappropriate, patients and families are able to review that with their health care provider and be able to make adjustments as necessary. I hope that answers the question, but please let me know if there's anything further I can add.

Dr. Fischer: Just a reminder to everyone to state your name before you-

Randi Oster: -Oh, sorry about that-

Dr. Fischer: -make a question.

Dr. Peiris: Thank you, Dr. Fischer. Vasum Peiris, CDRH.

Randi Oster: Randi Oster, Consumer Representative. Okay. Thank you.

Dr. Peiris: Thank you.

Committee Discussion and Vote (CDRH)

Dr. Fischer: Any other questions for Dr. Peiris? Okay. I don't see any other raised hands. Thank you. Thank you, Dr. Peiris. We will go ahead and proceed to the voting for CDRH. If we can move the slide to the voting question. Here we go. The voting question is being displayed on your screen. It states: "FDA recommends continuing routine, ongoing postmarket safety monitoring of each of the CDRH products under discussion." The question that we are being asked to answer today is: does the Pediatric Advisory Committee concur? The options are yes, no, abstain or recused. Are there any questions regarding specifically the wording of this question before we proceed? And go ahead and just raise your hand on the zoom platform, please, and state your name for the record. Mrs. Oster, go ahead.

Randi Oster: Yes. So, two of the products are no longer being monitored, the Flourish and the other, Pulserider. So, when we say yes, are we saying yes to the fact that we agree that these are no longer actively used?

Dr. Peiris: Dr. Fischer, can I answer the question?

Dr. Fischer: Yes. I was going to ask you to do so. Thank you.

Dr. Peiris: Happy to. Thank you again for clarifying, for bringing up that clarification point. And once again, Vasum Peiris, CDRH. As stated in both of the executive summaries for both of those devices, both devices are current- are no longer being marketed, and there was a request from the sponsors to discontinue marketing. So, for those two devices, we will no longer be providing any regular updates to the PAC, since they no longer will exist in the marketplace within the US. And the answer of "yes" to the to this question, this general question that's been developed is an answer of concurrence with our recommendation in the executive summaries.

Randi Oster: Okay. Thank you.

Dr. Fischer: Thank you. Any other questions regarding the wording or the voting? Dr. Krug, go ahead.

Dr. Krug: Hey, just-- Steve Krug. I'm a PAC member. Just a follow up to that. So, yeah, I noticed that, I presume, though you guys probably know this better than I do, that if for some reason a decision is made to resume marketing in the US again. Could you just let us know what then happens?

Dr. Peiris: Sure. Vasum Peiris, for the record. CDRH. Thanks, Steve for that question. If there is a request for resumption, which I'm going to go out on a limb and say that hasn't occurred, but if such a request does occur, we'll be happy to engage with the sponsor and clarify the path forward with them.

Dr. Fischer: Other questions for Dr. Peiris? Okay. With that, we will proceed with the question and open the question for any other further discussion. Please, go ahead and raise your hand. 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. Any other further questions before we take the vote before us?

Okay, so I see there's no further discussion. We will now begin the voting process. I would like to add, after votes are collected, PAC members will have the opportunity to summarize their votes into the record and state any reasoning behind your vote. At this time, all voting members of the PAC,

designated federal Officer and AV staff will enter the voting room, and all other meeting attendees will join a breakout room. At the conclusion of voting, the meeting will resume and everyone will filter into the main meeting room. The vote will then be displayed on the screen, and the DFO will read the vote from the screen into the record. I'd like to add, although the meeting is not officially on a break while the committee is voting, it's okay to step away during this time, but we do strongly recommend to not exit the meeting, as you will then be placed in a waiting room until the meeting resumes. And thank you everyone for your patience.

Welcome back everyone. It's Gwen Fischer. We are ready to see the results. If they could be displayed. And I will now turn the meeting over to our DFO.

Shivana Srivastava: Thank you, Dr. Fischer. This is Shivana Srivastava. For the voting question, "Does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine, ongoing post-market safety monitoring for each of the CDRH products under discussion?" The results are: For product Enterra-- My apologies. For product Contegra, there are ten yeses, zero noes, zero abstains, and one recusal. For product Enterra, there are nine yeses, one no, zero abstains and one recusal. For product Flourish, there are 11 yeses, zero noes, zero abstains and zero recusals. For product Pleximmune, there are 11 yeses, zero noes, zero abstains, and zero recusals. For Pulserider, there are 11 yeses, zero noes, zero abstains and zero recusals. For Sonalleve, there are 11 yeses, zero noes, zero abstains, and zero refusals. Thank you.

Please refer to the meeting minutes to see the tabular summary of how individual PAC members voted for each product. (This statement was added to the transcript to provide additional information for the reader)

Dr. Fischer: Thank you. Now that the voting for CDRH has been completed, we will go down the meeting roster and have everyone who voted state their name, their vote, and if you want to, you can add reasons for the reason that you voted into the record. Also of note, if you see an error, please correct it for the record. We will start with David Callahan.

Dr. Callahan: David Callahan. I voted yes.

Dr. Fischer: Thank you. Angela Czaja.

Dr. Czaja: I voted yes on all products.

Dr. Fischer: Douglas Diekema.

Dr. Diekema: I voted yes on all products.

Dr. Fischer: Charleta Guillory.

Dr. Guillory: I voted yes on all products.

Dr. Fischer: Richard Holubkov.

Dr. Holubkov: I was recused from voting on the Contegra and Enterra Therapy products, and I voted for on the other four products.

Dr. Fischer: Thank you. Bridgette Jones.

Dr. Jones: I voted yes on all products.

Dr. Fischer: Steven Krug.

Dr. Krug: Sorry, I couldn't get off mute. Steve Krug. I voted yes on all products. Thank you.

Dr. Fischer: Gianna McMillan.

Dr. McMillan: Gianna McMillan. I voted yes for all products.

Dr. Fischer: Roberto Ortiz-Aguayo.

Roberto Ortiz-Aguayo: Roberto Ortiz. I voted yes in all products.

Dr. Fischer: Randi Oster.

Randi Oster: This is Randi Oster. I voted yes for all products except for the Enterra. And specifically addressing the fact that there is the shock and the recommendation, especially after listening to the answer to the question when I asked: to follow the Baldrige process through the Department of Commerce, which is what is the approach for collecting the information? How do we deploy it? What are we learning and then integrating it? And I think there's an opportunity here. So, I voted no so that we can expand on the work that we're doing with this product.

Dr. Fischer: Thank you. And Michael White.

Dr. White: Michael White. I voted in agreement with the recommendations from CDRH on all the products.

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

Dr. Fischer: Okay. Thank you everyone. That wraps up our discussion and vote on the CDRH. Next slide please. We'll now be moving on to a discussion around CBER. We'll be focusing on pediatric focus, post-market safety reviews completed by the Center for Biologics Evaluation and Research, represented by Doctor Craig Zinderman. Dr. Zinderman, you have the floor.

Dr. Zinderman: Hi. Good afternoon. Craig Zinderman, CBER. Can we have the next slide? Okay. So, for CBER, we have three products: Agriflu, Cutaquig and Xyntha.

Clarifying Questions

Dr. Fischer: Okay. Thank you, Dr. Zinderman. We will now proceed with clarifying questions. I will remind you to use the raise hand button on the Zoom function so that I know to call on you. When called upon, please remember to state your name for the record before asking your question. Any clarifying questions for Dr. Zinderman? Dr. Holubkov, go ahead.

Dr. Holubkov: Hi Dr. Zinderman, thank you for these reports. I was- I was simply wondering; this is more of a technical question. I know parts of your- one component of your safety ascertainment system involves data- involves data mining, vaccine versus the others. I was simply wondering, are the technical are details of the data mining that you that you use, are they published somewhere in an article or perhaps some- perhaps some other FDA- other communication. Just out of interest, I have no I have no concerns by the way- about the way it was done in the reports that I read. Thank you.

Dr. Zinderman: Yeah. There are public there are publications that we've done. I don't know how detailed they get offhand for the time, but you can, you know, we can provide you some references, maybe after the meeting. But there are some publications about how that data mining is done. It's called an empirical Bayesian geometric mean. We use an arbitrary threshold of 2.0 times the lower bound of that empirical Bayesian 95% confidence interval. And I think that's what we have in the memo. It's the same measure that CDER uses as well. I don't know if they had data mining results in their memos, but it's the same tool that they use. Vaccine data mining has the same calculation, it is just calculated separately than data mining for FAERS data which includes all the drugs and other non-vaccine biologics.

Dr. Holubkov: Thanks.

Dr. Fischer: Thank you, Dr. Zinderman. There's a question from Dr. White. Please go ahead, Dr. White.

Dr. White: Just very quickly, the immunoglobulin given sub-Q. What are the volumes of those doses that they're speaking of? Is this like a normal subcutaneous injection, or is this more like clysis?

Dr. Zinderman: Yeah, the volume is variable. And there's a section in the prescribing information for Cutaquig that describes how to calculate it in various circumstances. So, it's actually highly variable depending on the patient's serum level. It also can depend on what products the patient is switching to the subcutaneous product from. If they're coming from an intravenous immunoglobulin, or they're coming from a subcutaneous product. It also depends on the frequency of administration. For instance, it's typically weekly. So, I can't give you like, exactly what the volume is, but I can give you-- Just, you know, for example-- And again, it's highly variable and it depends on the serum levels that are measured for that individual patient. But a patient who's, let's say a 70-kilogram adult, could be getting seven grams a week. That's just an example dose, if that's what that patient's serum levels sort of corresponded to when you do the calculations as described in the package insert.

Dr. White: What is that in volume?

Dr. Zinderman: It's 100 mg/kg. I'm not sure.

Dr. White: I understand, but what is the volume that's going to be injected into the patient subcutaneously?

Dr. Zinderman: I don't know that.

Dr. White: All right. Thank you.

Committee Discussion and Vote

Dr. Fischer: Other questions from the PAC for Dr. Zinderman regarding the CBER products? Okay. I don't see any other hands up. So, we can now proceed to voting for CBER. Thank you, Dr. Zinderman. We can go to next slide.

Committee Discussion and Vote (CBER)

The voting question is now up on your screen. It states: FDA recommends continuing ongoing post-market safety monitoring of each of the CBER products under discussion. The question we're being asked to answer today is: Does the Pediatric Advisory Committee concur? The options again are yes, no, abstain or recuse. Are there any questions from the PAC about the wording of the

question? If so, please raise your hand and state your name. Okay, I do not see any questions, so we will now proceed with the open question. I again remind public observers that while the meeting is open for public observation, public attendees may not participate except to the specific request of the panel. Are there any further clarifying questions on the voting question before us? Okay, if there is no further discussion, we can now begin the voting process.

I would like to add, after votes are collected, PAC members will have the opportunity to summarize their votes into the record and state any reasoning behind your vote. At this time, all voting members of the PAC, the DFO and AV staff will enter the voting room and all other attendees will join a breakout room. At the conclusion of voting, the meeting will resume and everyone will filter into the main meeting room again. The vote will then be displayed on the screen, and the DFO will read the vote from the screen into the record. I'd like to add, although the meeting is not officially on a break while the committee is voting, this is a good time to step away if you need to. However, we strongly recommend to not exit the meeting. If you do choose to exit, you will be placed in a waiting room until the meeting resumes. Thank you for your patience.

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

Shivana Srivastava: Thank you, Doctor Fischer. This is Shivana Srivastava. For the voting question: Does the Pediatric Advisory Committee concur with FDA's recommendation to continue routine, ongoing post-marketing safety- apologies to continue routine, ongoing post-market safety monitoring for each of the CBER products under discussion. The results are:

For Agriflu, there are ten yeses, zero noes, zero abstains, and one recusal. For Cutaquig, there are 11 yeses, zero noes, zero abstains and zero recusals. For Xyntha, there are nine yeses, zero noes, zero abstains, and two recusals. Thank you.

Please refer to the meeting minutes to see the tabular summary of how individual PAC members voted for each product. (This statement was added to the transcript to provide additional information for the reader)

Dr. Fischer: Thank you. Now that voting for CBER has been completed, we will go down the meeting roster and have everyone who voted state their name, their vote. And if you want to, you can state the

reason why you voted as you did into the record. If you do see an error, please correct it for the record. We will start with David Callahan.

Dr. Callahan: This is David Callahan. I voted yes for Cutaquig and was recused from voting for the other two products.

Dr. Fischer: Thank you. Angela Czaja.

Dr. Czaja: Angela Czaja. I voted yes on all products.

Dr. Fischer: Thank you. Douglas Diekema.

Dr. Diekema: Doug Diekema. I voted yes on all three products.

Dr. Fischer: Charleta Guillory.

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

Dr. Fischer: Thank you. Richard Holubkov.

Dr. Holubkov: All right. Rich Holubkov. I voted yes on Agriflu and Cutaquig, and recused for Xyntha.

Dr. Fischer: Thank you. Bridgette Jones.

Dr. Jones: Bridgette Jones. I voted yes on all products.

Dr. Fischer: Steven Krug.

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

Dr. Fischer: Gianna McMillan.

Dr. McMillan: Gianna McMillan. I voted yes for all projects.

Dr. Fischer: Roberto Ortiz.

Roberto Ortiz-Aguayo: Roberto Ortiz. I voted yes on all products.

Dr. Fischer: Randi Oster.

Randi Oster: This is Randi Oster. I voted yes on all products.

Dr. Fischer: And Michael White.

Dr. White: Michael White. I voted yes on all three. Thank you.

Dr. Fischer: All right. Thank you everyone. We can move to the next slide. That concludes our CBER voting process as well as the Pediatric Advisory Committee Day. I want to thank everyone for participating. Before we conclude this meeting, I would like to thank the members of the PAC for their engaging discussion and their participation, as well as the time they spent reviewing materials

beforehand. I also want to thank the members of the FDA for their efforts bringing excellent background materials to us and as well as their presentations done today. With that, I will bring this meeting to a conclusion and thank everyone for their participation. And we will now adjourn this meeting.

Thank you everyone.