FOOD AND DRUG ADMINISTRATION (FDA)
Office of Pediatric Therapeutics
Pediatric Advisory Committee (PAC) Meeting

OPEN SESSION

September 15, 2020

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

ATTENDEES

PAC DESIGNATED FEDERAL OFFICER	Robert Dracker, M.D., M.H.A., M.B.A., C.P.I.
Marieann Brill, MBA, RAC, MT(ASCP)	Gwyneth Fischer, M.D., F.A.A.P.
PAC MEMBERS	Bridgette Jones, M.D., M.S., F.A.A.A.A.I., F.A.A.P.
Kelly Wade, M.D., Ph.D.	Olcay Jones, M.D., Ph.D.
Premchand Anne, M.D., M.B.A., M.P.H., F.A.C.C.	Jeffrey Lukish, M.D., F.A.C.S., F.A.A.P.
David Callahan, M.D.	James McGough, M.D.
Melody Cunningham, M.D., F.A.A.H.P.M.	Gianna McMillan, DBe
Randall Flick, M.D., M.P.H.	Jennifer Plumb, M.D., M.P.H.
Peter Havens, M.D., M.S.	Jeffrey Strawn, M.D.
Sarah Hoehn, M.D., M.Be., F.A.A.P.	FDA PRESENTERS
Richard Holubkov, Ph.D.	Ivone Kim, M.D.
Roberto Ortiz-Aguayo, M.D., M.M.M.	Carmen Cheng, Ph.D.
Randi Oster, M.B.A.	Mohamed A. Mohamoud, Pharm.D., M.P.H., B.C.P.S.
Wael Sayej, M.D., M.B.A., F.A.A.P.	Lisa Harinstein, Pharm.D., B.C.C.C.P.
Christy Turer, M.D., M.H.S., F.A.A.P., F.T.O.S.	Craig Zinderman, M.D., M.P.H.
Benjamin Wilfond, M.D.	Priya Venkataraman-Rao, M.D.
PAC MEMBERS (Non-Voting)	SPONSOR PRESENTERS
Jennifer Goldman, M.D., M.S.	Ted Heise, Ph.D., RAC
Ronald Portman, M.D., F.A.A.P.	Mario Zaritzky, MD
TEMPORARY MEMBERS (Voting)	Bethany Slater, MD
Angela Czaja, M.D., M.Sc.	

FDA PARTICIPANTS	OPEN PUBLIC SPEAKER
Susan McCune, M.D.	Diana Zuckerman, Ph.D.
Ethan Hausman, M.D.	
Doris Auth, Pharm.D.	
Andrew D. Mosholder, M.D., M.P.H.	
Qi Chen, M.D., M.P.H.	
Barbara Buch, M.D.	
Adrienne Hornatko-Munoz, RAC	
Narayan Nair, M.D.	
Jonathan Reich, M.D., M.S.	
Dorothy Scott, M.D.	
Vasum Peiris, M.D., M.P.H., F.A.A.P., F.A.C.C., F.A.S.E	
Mark Antonino, M.S.	
Shani Haugen, Ph.D.	

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OPENING REMARKS:

CALL TO ORDER, INTRO OF COMMITTEE

DR. WADE: Good morning everyone and welcome. I would first like to remind everyone to please mute your telephone lines when you are not speaking. For media and press, the FDA press contact is Gloria Sanchez-Contreras. Her email is gloria.sanchez-contreras@fda.hhs.gov. Her telephone number is 301-796-7686. For industry and press, please send an email to the PAC, pac@fda.hhs.gov. The information is now shown on the screen.

My name is Kelly Wade, and I will be chairing today's virtual meeting. I will now call today's meeting of the Pediatric Advisory Committee to order. We will start by going down the meeting roster and introducing ourselves. When I call your name, please introduce yourself.

To begin with, my name is Kelly Wade. I am a neonatologist for Children's Hospital of Philadelphia. I will now go through the Pediatric Advisory Committee

roster in alphabetical order. Premchand Anne?

DR. ANNE: This is Premchand Anne. I'm a pediatric cardiologist at Ascension St. John Children's Hospital in Detroit, Michigan.

DR. WADE: David Callahan? Please remember to unmute your phone.

DR. CALLAHAN: My name is David Callahan. I'm a pediatric neurologist at Washington University School of Medicine in St. Louis.

DR. WADE: Thank you. Melody Cunningham?

DR. CUNNINGHAM: I'm Melody Cunningham, pediatric palliative care and medicine at University of Tennessee, previously pediatric hematology/oncology.

DR. WADE: Great. Angela Czaja?

DR. CZAJA: I'm Angela Czaja. I'm a pediatric critical care physician and a pharmacoepidemiologist from the University of Colorado Children's Hospital, Colorado.

DR. WADE: Thank you. I'm sorry about that name pronunciation. Robert Dracker?

DR. DRACKER: Bob Dracker, pediatrics and

hematology at SUNY Health Science Center in Syracuse.

DR. WADE: Gwyneth Fischer?

DR. FISCHER: Hi, Gwen Fischer from the University of Minnesota Pediatric Critical Care.

DR. WADE: Welcome. Randall Flick?

DR. FLICK: Randall Flick, Mayo Clinic pediatric anesthesia and critical care.

DR. WADE: Jennifer Goldman?

DR. GOLDMAN: Hi, Jen Goldman, pediatric infectious diseases and clinical pharmacology at Children's Mercy in Kansas City.

DR. WADE: Peter Havens?

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

DR. WADE: Sarah Hoehn?

DR. HOEHN: Sarah Hoehn, pediatric critical care medicine and pediatric hospice and palliative care, University of Chicago Children's Hospital in Chicago, Illinois.

DR. WADE: Richard Holubkov?

DR. HOLUBKOV: Hi, Rich Holubkov. I'm a biostatistician, faculty member at the Department of Pediatrics, University of Utah's School of Medicine, Salt Lake City.

DR. WADE: Thank you. Bridgette Jones?

DR. B. JONES: Bridgette Jones. I'm a pediatric allergy/asthma immunologist and clinical pharmacologist at Children's Mercy Hospital in Kansas City.

DR. WADE: Olcay Jones?

DR. O. JONES: Good morning. This is Olcay Jones, Pediatric Rheumatology, Walter Reed Military Medical Center, Bethesda.

DR. WADE: Jeffrey Lukish?

DR. LUKISH: Good morning, everyone. Jeffrey Lukish, pediatric surgeon, Children's National Washington, D.C.

DR. WADE: James McGough?

DR. McGOUGH: Hi, Jim McGough, child and adolescent psychiatrist, professor of clinical psychiatry at UCLA.

DR. WADE: Gianna McMillan?

DR. McMILLAN: Gigi McMillan, Professor of Research Ethics at Loyola Marymount University and patient representative.

DR. WADE: Great. Roberto Ortiz-Aguayo?

DR. ORTIZ-AGUAYO: Roberto Ortiz-Aguayo, child and adolescent psychiatry, Children's Hospital of Philadelphia.

DR. WADE: Randi Oster? You may need to remember to unmute your phone.

MS. OSTER: Well, I should be -- can you hear me now?

DR. WADE: Yeah.

MS. OSTER: Okay. This is Randi Oster. I am the consumer representative and the President of Help Me Health.

DR. WADE: Thank you. Jennifer Plumb?

DR. PLUMB: Jennifer Plumb, pediatric emergency medicine, University of Utah Department of Pediatrics.

DR. WADE: Great. Ron Portman?

DR. PORTMAN: I'm Ron Portman, pediatric nephrologist, Pediatric Clinical Development head at Novartis Pharmaceutical.

DR. WADE: Wael Sayej? We're not hearing you yet, Dr. Sayej.

DR. SAYEJ: This is Dr. Wael Sayej. I'm a pediatric gastroenterologist at Baystate Children's Hospital, in Springfield, Massachusetts.

DR. WADE: Great. Thank you. Jeffrey Strawn?

DR. STRAWN: Good morning, I'm Jeff Strawn. I'm a child and adolescent psychiatrist and also have an appointment in clinical pharmacology here at the University of Cincinnati and Cincinnati Children's in Cincinnati, Ohio.

DR. WADE: Welcome. Christy Turer?

DR. TURER: Hi. This is Christy Turer. I am a combined internal medicine and pediatrician with a board certification in obesity medicine. I'm at UT Southwestern in Dallas, Texas.

DR. WADE: And Benjamin Wilfond.

DR. WILFOND: Hi, this is Ben Wilfond. I am a

pediatric pulmonologist at Seattle Children's, and I'm also the Division Chief for Bioethics and Palliative Care at the Department of Pediatrics, University of Washington.

DR. WADE: Great. Moving on to the FDA representatives, Marieann Brill?

MS. BRILL: Hello, good morning. This is Marieann Brill. I am the DFO for this meeting. Thank you.

DR. WADE: Suzie McCune?

DR. McCUNE: Good morning, my name is Susan McCune, and I'm the Director of the Office of Pediatric Therapeutics.

DR. WADE: And Ethan Hausman.

DR. HAUSMAN: Good morning. My name is Ethan Hausman. I am a pediatrician and pathologist, and I am a clinical reviewer in the Division of Pediatric and Maternal Health.

DR. WADE: Great. Moving forward, there are often strongly held opinions regarding the topics being discussed at today's meeting. Our goal is that today's

meeting will be an open and fair forum for the discussion of the planned topics, ensuring individuals can express their views without interruption. This is 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 Federal Advisory Committee Act, and the government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you. Now I will pass it to Marieann Brill who will read the Conflicts of Interest Statement.

CONFLICT OF INTEREST STATEMENT

MS. BRILL: Good morning. The Food and Drug Administration is convening today, September 15, 2020, for a meeting of the Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972, Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act of 2003, the Food and Drug Administration Amendments Act of 2007, and the Food and Drug Administration Safety and Innovation Act of 2012. Today's meeting is a particular matter involving specific parties during which the Committee will discuss Vyvanse, Mydayis, Adzenys ER, Orencia, Gamunex-C, and Flourish. The Committee will discuss acute dystonia associated with the use of attention deficit hyperactivity disorder, ADHD, medications, including methylphenidate products, amphetamine products, and atomoxetine. Additionally, the Committee will discuss acute hyperkinetic movement disorder associated with the combined use of ADHD stimulants and antipsychotics, including first-generation

antipsychotics and second-generation antipsychotics.

The Chairperson for today's meeting is Dr. Kelly Wade. With the exception of the industry representative, all standing and temporary voting 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, 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

Related to the discussions at today's meeting, standing and temporary voting members of the Committee who are special government employees or regular government employees 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 purposes of 18 U.S.C. Section 208, their employers. These interests may

include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that members and temporary voting members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S.C. Section 208. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved 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 meeting and all financial interests reported by the Committee

members and temporary voting members, and in accordance with 18 USC Section 208 (b)(3), a waiver has been granted to Dr. Strawn for his institution's research contract study, in which he serves as a sub-investigator. A waiver allows an individual to participate fully in the Committee's deliberations. FDA's reasons for issuing a waiver are described in the waiver document, which is posted on FDA's website under the appropriate product class or committee at www.fda.gov/advisorycommittees/committeesmeetingmaterials/. Copies of waivers may also be obtained by submitting a written request to the Agency's Division of Freedom of Information at 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857 or via fax to 301-827-9267.

With respect to the meeting's consumer, patient, and pediatric health organization representatives, we would like to disclose that Ms. Oster is participating in this meeting as a voting representative acting on behalf of consumers and not to any particular organization. Dr. McMillan is

participating in this meeting as a voting representative acting on behalf of patients and not to any particular organization. And Dr. Goldman is participating in this meeting as a non-voting representative acting on behalf of pediatric health organizations.

The consumer, patient, and pediatric health organization representatives are special government employees, and as such, have been screened for conflicts of interest. With respect to the meeting's industry representative, we would like to disclose that Dr. Portman is participating in this meeting as a non-voting representative acting on behalf of regulated industry. Dr. Portman is not a regular or special government employee, and as such, has not been screened for conflicts of interest.

For today's meeting Dr. Czaja, Dr. Dracker, Dr. Fischer, Dr. Bridgette Jones, Dr. Olcay Jones, Dr. Lukish, Dr. McGough, Dr. McMillan, Dr. Plumb, and Dr. Strawn will be serving as temporary voting members. We would like to remind standing and temporary voting and

non-voting members that if the discussions involve any other firms or products not already on the agenda for which a participant has a personal or imputed financial interest, the participants need to exclude themselves from such discussions and their exclusion will be noted for the record. FDA also encourages all other meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships that you may have with the sponsor, its product, and, if known, competing firms and products.

This concludes my reading of the conflict of interest statement for the public record. At this time, I would like to hand over the meeting to Dr. Wade. Thank you.

DR. WADE: Thank you. We will now proceed with the opening remarks from Dr. Suzie McCune, Director of the Office of Pediatric Therapeutics.

FDA OPENING REMARKS

DR. McCUNE: Good morning, everyone. I'm Suzie McCune. We've met before. I'm the Director in

the Office of Pediatric Therapeutics in the Office of Clinical Policy and Programs in the Office of the Commissioner at the FDA. We are here today to discuss pediatric adverse reports following pediatric labeling changes as legislatively mandated, discussing four products from the Center for Drug Evaluation and Research, or CDER; one product from the Center for Biologics Evaluation and Research, or CBER; and one product from the Center for Devices and Radiological Health, or CDRH.

First, I want to thank you for joining us virtually, and I hope that you and your families are healthy in this time of COVID-19. We are used to doing these meetings in person, and the transition to an all virtual meeting is challenging. I want to thank Marieann Brill and her team for working hard to ensure that the meeting will be seamless. However, as we all know, technology has a mind of its own, and we expect that there may be some challenges today. We have worked to provide backup solutions if there are any issues. I ask that you approach the day with openness

and flexibility.

With that, let's get the day going. I will provide a few opening remarks and then turn the meeting over to Dr. Kelly Wade. I want to do a personnel update, a summary of the web-posted reviews, an update of Montelukast that was discussed at the last PAC meeting, and presentation of the non-compliance letters. For the personnel update, I want to start with an introduction of Dr. Jennifer Goldman, who is joining the PAC as Pediatric Health Organization representative.

Dr. Goldman is an Associate Professor at the University of Missouri Kansas City and a member of the Department of Pediatrics Division of Pediatric Infectious Diseases and Clinical Pharmacology at Children's Mercy Hospital in Kansas City. She completed her medical school at the University of Kansas School of Medicine and residency and fellowship at Children's Mercy Hospital. Pease join me in welcoming Dr. Goldman to the PAC.

The next four individuals are from the Office

of Pediatric Therapeutics. It is with a very heavy heart that we are saying goodbye to Sheila Reese as she has decided to retire. Most of you have worked with Sheila over the years with respect to conflict of interest.

Sheila completed her education at the University of Rochester and her nursing diploma from the Holy Name Hospital School of Nursing in Teaneck, New Jersey. Her nursing career included care in psychiatry, adolescent psychiatry, and adolescent medicine followed by experience as a director of utilization review and then as a treatment coordinator for workmen's compensation. Her career took her from Saratoga, New York to Rochester, New York; Yale; New Haven; Case Western Reserve; Toledo, Ohio; and Washington, D.C. We were lucky to recruit her to join the Office of Pediatric Therapeutics in 2011. She worked on all aspects of PAC logistics, specifically in the conflict of interest arena. We will miss Sheila dreadfully, but we wish her all the best in her upcoming retirement.

The next three individuals are new additions to the Office of Pediatric Therapeutics, or OPT, who will be working with the PAC. Ester Hatton is joining us as a Regulatory Health Project Manager and health scientist. Ester's experience includes work in pharmacy operations in the Department of Defense, and she comes to OPT from the FDA Center for Tobacco Products Office of Science where she was a reviewer and regulatory health project manager.

Jeanine Best is a pediatric nurse practitioner who has been at the FDA for 21 years with the majority of her time spent in the Division of Pediatric and Maternal Health in CDER before recently moving to OPT as a Senior Health Scientist. Prior to the FDA, Jeanine held various clinical positions at Children's National Medical Center, Secondary School for the Deaf at Gallaudet University, and the University of Maryland Medical Center.

Commander Margaret Caulk is joining OPT as a Health Science Administrator. She completed her undergraduate degree at Colgate University with a

Master's of Public Health in International Health and Environmental Health from Boston University. She joined the FDA eight years ago. She has worked in the areas of emergency preparedness working with vulnerable populations, drug safety, and drug supply chain preservation. Please join me in wishing Sheila all the best in her retirement and in welcoming Ester, Jeanine, and Margaret to OPT.

Next, I want to highlight the web-posted reviews. Since we were not able to have the PAC meeting in the spring, we are including the reviews for both the spring and the fall of 2020. There are 15 CDER products, nine CBER products, and seven CDRH products. The docket for comments on these reviews is open and will remain open until September 20th, 2020.

Next, I wanted to give the PAC an update on activities related to Montelukast and the neuropsychiatric events that were presented at the last PAC meeting. Just to review, in 2008 the Warnings and Precautions section of the labeling was updated, and Drug Safety Communication and Dear Health Care Provider

letters were issued. These were based on post-marketing reports that included a wide variety of events including behavior changes and completed suicides. Between 2008 and 2019, additional neuropsychiatric events were included in the label.

In September 2019, we had a joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Mitigation Advisory Committee in response to stakeholder requests. At that time, we reviewed FAERS data, published literature, and the results from an observational study in Sentinel. Based on the PAC discussions, there was a reassessment of the benefit-risk for asthma and allergic rhinitis. This included a discussion that the benefits may not outweigh the risks for the treatment for allergic rhinitis based on new safety information, the nature of the disease, and the context of available therapies. Based on all of this information, on March 4th, 2020 the FDA issued safety labeling changes that included a boxed warning, a limitation of use for allergic rhinitis to reserve the use for patients who have inadequate response or

intolerance to alternative therapies, a medication guide, and a drug safety communication and press release. I have provided the link to all of this information at the bottom of the slide.

I am also required by the legislation to report on non-compliance letters. There are currently two for CBER and 46 for CDER. The website provides the list of the sponsor, the product, a copy of the non-compliance letter, the sponsor's response if available, and the status of the PREA requirement, for example, released, replaced, or fulfilled.

Since the last time I reported to the PAC on these, there are no new letters for CBER and 15 new letters for CDER. The information on these 15 new letters is listed on Slides 9, here, and 10. These are all posted on the website. With that I would like to welcome you to the fall 2020 PAC meeting and keeping patience and flexibility in mind, I will turn the meeting over to Dr. Wade.

DR. WADE: Thank you, Suzie. Thank you for that update on the follow up and welcome to our newest

members in the OPT. Moving forward to the FDA presentations from CDER, both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. And to ensure such transparency at the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the 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 interests 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 pre-recorded

presentations from the FDA. Please ensure at this time that your computer speakers are turned up in your computer settings for this portion of the meeting.

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER) STANDARD REVIEW OF ADVERSE EVENT PRESENTATION

VYVANSE (LISDEXAMFETAMINE DIMESYLATE)

DR. KIM: -- Division of Pharmacovigilance in CDER's Office of Surveillance and Epidemiology. Today I'll be presenting the Vyvanse, or lisdexamfetamine, pediatric-focused safety review. This is the outline of my talk, and we will begin with some background information.

Lisdexamfetamine is a central nervous system stimulant. It received initial market approval in February 2007, and it's currently approved for the treatment of attention deficit hyperactivity disorder, or ADHD, and moderate to severe binge eating disorder in adults. The initial approval for lisdexamfetamine included the indications to treat ADHD in children six to 12 years old. In 2010, FDA extended the approval

for the treatment of ADHD in adolescents 13 to 17 years old. And the indication was expanded again in 2013 for the maintenance treatment of ADHD in patients six to 17 years old.

In 2017, FDA approved chewable tablets, a new formulation for the treatment of ADHD in patients six years and older. It was the approval of this new formulation that led to a pediatric labeling change that triggered the current review. FDA previously presented pediatric-focused safety reviews on lisdexamfetamine to the PAC in 2012 and 2016. The 2012 evaluation did not identify any new safety concerns, and the Committee recommended returning to standard, ongoing monitoring for adverse events.

In 2016, FDA presented another pediatric-focused safety evaluation that identified a potential signal of alopecia and recommended to perform a review of this event. The Committee members agreed with plans to continue ongoing safety monitoring and to review the safety signal for alopecia and bring the information to the Committee at a future date. And although FDA did

not identify a signal for suicidality, the Committee discussed post-marketing cases identified within the review, and the PAC recommended that FDA should explore the use of claims databases to obtain the information regarding suicidality.

Subsequent to the 2016 PAC presentation, FDA completed a post-marketing safety review of alopecia in selected amphetamine products that were not previously labeled for those events. And this included lisdexamfetamine. In May 2017, alopecia was added to the Adverse Reactions Post-Marketing Experience section of the labeling for those selected products.

In order to develop improved methodologies for studying intentional self-harm in the association with drug exposures, colleagues in the Division of Epidemiology, or DEPI, launched the Data Sources for Suicide Outcomes Project sponsored by the Safety Interest Research Group. The project includes evaluation of multiple drug products. And one outcome of the project was a published systematic review of suicidal outcomes definitions in observational studies.

This published evaluation found that many observational studies had poor sensitivity or poor positive predictive value. Overall, methodologies for studying suicide-related outcomes is currently not well established, and low event rates present challenges regarding statistical power. The following is a brief review of the relevant pediatric labeling.

Lisdexamfetamine's labeling contains the warnings and precautions listed here for your reference. Adverse reactions in pediatric patients derive from clinical trials and were similar for children, adolescents, and adults. Most frequently reported adverse reactions were gastrointestinal events such as anorexia, decrease in appetite, decreased weight, dry mouth, upper abdominal pain, nausea, vomiting, and diarrhea. We will begin the presentation of our pediatric assessment with analysis of drug use trends.

In this figure, we show the estimated number of pediatric patients age zero to 17 years old who received dispensed prescriptions for lisdexamfetamine

products in each 12-month period during July 2015 through June 2019. During the study period, approximately 2 million total patients of all ages received dispensed prescriptions for lisdexamfetamine products annually, and approximately 45 percent were pediatric patients younger than 18 years old. Focusing on the most recent 12-month period ending in June 2019, approximately 850,000 pediatric patients age zero to 17 years received dispensed prescriptions for lisdexamfetamine. And of these, approximately 60 percent were age 12 to 17 years, 45 percent were age six to 11 years, and 1 percent were zero to five years old.

Now, we'll share our evaluation of the FDA Adverse Event Reporting System data, or FAERS data, in the following slides. We searched the FAERS database from the period of July 1st, 2015 through April 30th, 2019 for domestic pediatric reports coded with a serious outcome. We excluded reports from further review if they were duplicate, reported labeled adverse events, were unassessable, described transplacental

exposure, did not describe adverse events, if the reports were unlikely to be related to lisdexamfetamine use, reported drug ineffective and indication-related adverse events, or if they had a miscoded age.

Consequently, we identified 23 cases with unlabeled serious adverse events for further analyses. Of the 23 cases with unlabeled serious adverse events, there were three cases reporting a fatal outcome, and the cases included a 17-year-old female with a history of unspecified mental disorder who completed suicide. Concomitant medications included an atypical antipsychotic, a benzodiazepine, and another unspecified medication.

Another case described a 15-year-old male who completed suicide while on therapy for lisdexamfetamine and methamphetamine dextroamphetamine. And the third case described a 15-year-old male with a history of conduct disorder who completed suicide. All cases had limitations, the most notable of which was missing information including other risk factors for suicide, details about concomitant medications, and temporality

of events relative to lisdexamfetamine use.

Twenty cases were coded with non-fatal outcomes. The most frequently reported adverse events were suicidal and self-injurious behavior and ideation. But there's insufficient evidence to support a signal with the identified cases as all of them had some degree of missing clinical information to allow for robust case assessments. And some cases described other risk factors for suicide or self-injury. This is consistent with findings from past evaluations of suicide-related events with lisdexamfetamine and other ADHD medications. These evaluations include placebo-controlled trials using prospective assessments for suicidal ideation behavior, such as the Columbia Suicide Severity Rating Scale.

These trials failed to provide evidence that lisdexamfetamine and other ADHD stimulants increased a risk for suicide-related events. There were applicant-completed reviews for suicide-related events with lisdexamfetamine that did not identify an increased risk for these events relative to the background risk

in the general population or the population of ADHD patients. And finally, there were FDA-completed reviews of suicide-related events and lisdexamfetamine and other ADHD drugs that also did not support a signal.

Among the serious unlabeled adverse events with non-fatal outcomes there were single reports of each: cerebrovascular accident, macular degeneration, aphthous ulcer, and elevated hepatic enzymes. Causality assessment was limited by lack of clinical information. An exploratory evaluation of FAERS data did not indicate that these were new safety signals.

Finally, we identified two cases that were consistent with acute dystonia. Acute dystonia was a monitored adverse event of interest during ongoing surveillance activities for all ADHD stimulants. Concurrent with our pediatric-focused safety review of lisdexamfetamine, the Division of Psychiatry and the Division of Pharmacovigilance initiated the evaluation of post-market data for evidence of acute hyperkinetic movements associated with a drug interaction between

methylphenidate and antipsychotic medication.

To ensure that the potential drug interaction was not driven by dystonic reaction induced by ADHD medication, the Division of Pharmacovigilance planned an evaluation of acute dystonia and ADHD medication. Therefore, although this pediatric-focused review identified a low number of cases of acute dystonia, we considered this a potential safety signal for further study. The acute dystonia cases included a case describing a 26-month-old male with accidental ingestion of lisdexamfetamine who then developed irritability, gait disturbance, hypertension, tachycardia, and dystonia. He received diphenhydramine and lorazepam in the emergency room and dexmedetomidine in the pediatric intensive care unit. The event outcome was not reported.

In the second case, it described an 11-year-old male with ADHD who recently restarted lisdexamfetamine after a brief discontinuation for school summer break. This child developed symptoms notable for hand tightness and inability to relax his

hands from the flexed position, episodes of being hunched over and hyperventilating, and he became limp and developed nystagmus. He was hospitalized, and the events resolved after treatment with an unknown medication. Lisdexamfetamine was discontinued with plans to switch to another treatment.

In summary, we identified acute dystonic reactions as a potential signal with lisdexamfetamine. Overall, our review of adverse events reported in pediatric patients identified events consistent with known events described in labeling. There was insufficient evidence to suggest a causal association with lisdexamfetamine and the remaining unlabeled adverse events evaluated. FDA recommends to continue ongoing post-marketing pharmacovigilance for all adverse events with lisdexamfetamine.

To assess the potential signal of acute dystonia identified with our pediatric-focused safety review, we conducted a full safety review through assessment of the FAERS database and the medical literature for reports and epidemiologic data of acute

dystonia with ADHD medication. The evaluation focused on ADHD stimulant medications, including amphetamines and methylphenidate and atomoxetine due to similarities in the mechanism of action. ADHD stimulants and atomoxetine are not labeled for acute dystonia, but ADHD stimulants are labeled for other acute hyperkinetic movement disorders, including dyskinesia, tremor, and ticks. And atomoxetine is labeled for ticks in the Adverse Reaction sections of their product labelings. Relevant information from the Adverse Reaction section of a representative amphetamine and methylphenidate product are here for your reference.

To conduct our analyses, we researched the FAERS data for all reports suggestive of dystonic symptoms received by FDA through December 6, 2019. And we identified cases for further analysis using the following inclusion and exclusion criteria. Cases were included if they met at least one of the inclusion criteria. And they were excluded if they met at least one of the exclusion criteria.

After accounting for duplicate reports and

applying the case selection criteria listed in the previous slide, we included 14 cases in the case series of acute dystonia with ADHD medication. Additionally, we performed a search of the medical literature for additional cases. But after applying our case selection criteria, we identified no additional cases for inclusion.

In this slide we present descriptive characteristics of cases of acute dystonia with ADHD stimulant medication or atomoxetine in FAERS.

All 14 cases involved pediatric patients. This may reflect differential rates of ADHD recognition and therefore treatment in children versus adults, and more cases reported male patients which is consistent with the higher prevalence of ADHD in males versus females. The total number of reports increased over time consistent with an increase in overall reporting of the FAERS by year. Most cases reported medication use as prescribed, with one case reporting accidental ingestion of a methylphenidate product that was not prescribed.

There were four cases reporting positive dechallenge, although in three of these cases symptom resolution resulted from ADHD drug withdrawal in addition to therapeutic interventions for the dystonic reaction. With regards to causality, three cases were assessed as probable causality for acute dystonia and ADHD medication. Of note, all three probable cases involved inappropriate ADHD medication dosages.

Eleven cases were assessed as having possible causality, and most of the possible cases also reported concomitant medications that were labeled for events such as dyskinesia or muscle cramps and spasms that could explain reported adverse events. A variety of factors, notably an inconsistency in the level of case detail, limited the vigorous assessment of events, and, therefore, we could not rule out other hyperkinetic movement disorders or other risk factors with certainty in all cases. And of the 14 cases, 13 were coded as serious.

The search of the medical literature for epidemiologic data of acute dystonia associated with

ADHD stimulants or atomoxetine identified three articles of interest. On balance, the epidemiologic literature did not provide much information on the occurrence of dystonia and ADHD medications. The Meyers study was a claims-based, observational retrospective cohort study that suggested that the incidence of dystonia is similar with pediatric use of stimulants or atomoxetine. However, it did not determine an incidence in unexposed patients, so there could be a roughly equal risk for both treatments. Also, lack of information regarding the accuracy of the outcome definition in the claims-based study makes it difficult to interpret the incident rates reported. Then the publication described a population-based study that did not indicate that the stimulant use was an important cause of dystonias in the population.

And finally, Sharp and Perdue published a cross-sectional study that found the combination of stimulants plus an atypical antipsychotic was associated with a more abnormal motor movement (Inaudible) epidemiologic literature for -- who

published a cross-sectional study (Inaudible).

MR. BONNER: This is Derek Bonner with the A/V team. Looks like we're having a little bit of issues with the playback of the video. I have loaded up the backup presentation. If you would like to just present live, that would be great.

DR. CHENG: Hi, this is Carmen Cheng. I'm a team leader in the Division of Pharmacovigilance. Ivone is not here today, and I can present for her. Let me advance the slides. We're almost at the end.

(Pause)

Okay. It's -- is there a way you can help me advance to where we were, further along? It's getting stuck.

MR. BONNER: The backup presentation that we have ends at Slide 39.

DR. CHENG: Oh, okay. Maybe this is -- sorry, this must be the -- okay. We're in the end. Okay. Let me go back. Okay. I'll start over from here.

The search of the medical literature for epidemiologic data of acute dystonia associated with

ADHD stimulants or atomoxetine identified three articles of interest. On balance, the epidemiologic literature did not provide much information on the occurrence of dystonia with ADHD medications. The Meyers study was a claims-based, observational retrospective cohort study that suggested the incidence of dystonia is similar with pediatric use of atomoxetine or stimulants. However, it did not determine an incidence in unexposed patients, so there could be a roughly equal risk for both treatments. Also, lack of information regarding the accuracy of the outcome definition in the claims-based study makes it difficult to interpret the incidence rates reported.

The Nutt publication described a population-based study that did not indicate that stimulant use was an important cause of dystonia in the population. Lastly, the Sharp and Purdue publication on a cross-sectional study found the combination of stimulants plus an atypical antipsychotic was associated with more abnormal motor movement. However, the study did not specifically study dystonia. Because of the cross-

sectional design of the study, those findings should be regarded as hypothesis generating aspects.

In conclusion, we found insufficient evidence to support the post-market safety signal of acute dystonia associated with ADHD stimulants or atomoxetine at this time. We identified a low number of cases in our FAERS case series. The totality of FAERS cases does not have the strength to support the association between acute dystonia and ADHD stimulants or atomoxetine. Information from the published epidemiologic literature on the risk of dystonia with ADHD drugs is limited and by itself does not permit conclusions to be drawn.

We conclude our presentation, and we'd like to acknowledge those listed on the slide who helped with the review or the presentation. Thank you.

DR. McCUNE: So this is Suzie McCune. I want to thank Carmen for stepping in, in that spirit of patience and flexibility. Thank you all so much. And I believe, Dr. Wade, were we going to do clarifying questions -- just clarifying questions for Carmen

because we'll have discussion for this later in the day?

(Pause)

Oh, this is Suzie McCune again, just be patient with us for a few minutes. We're just -- to get all of the A/V information back on track.

(Pause)

This is Suzie McCune again. I just wanted to make sure, Dr. Wade, are you able to hear us? Dr. Wade, I believe you might be on mute. Ah, great. I think we can hear you.

DR. WADE: Thank you. Yes. Thank you, members of the audio/visual team. There were double mutes happening there. So we're going to move on to Dr. Mo's presentation of the pediatric-focused safety review, and this presentation audio will be through your phone.

DR. MOHAMOUD: Yes, can you hear me?

DR. WADE: Yes.

MYDAYIS (MIXED SALTS OF A SINGLE-ENTITY AMPHETAMINE PRODUCT) AND ADZENYS ER (AMPHETAMINE)

DR. MOHAMOUD: Okay. Good morning and welcome to the members of the Pediatric Advisory Committee. My name is Mohamed Mohamoud. I'm a safety evaluator in the Division of Pharmacovigilance within CDER's Office of Surveillance and Epidemiology. Today I'll be presenting the pediatric-focused safety review of Mydayis and Adzenys ER. Next slide, please?

The outline of my presentation will be as follows. I'll begin the presentation with background information on Mydayis and Adzenys ER, including the pediatric labeling history that triggered this review, and previous amphetamine pediatric postmarketing safety reviews presented to the PAC. Then, I will share drug utilization data for amphetamines in pediatric patients within the United States.

I will then present post-marketing safety data obtained from the FDA Adverse Event Reporting System, also known as FAERS. I will then share findings from

an evaluation of a newly identified safety signal identified during this pediatric-focused review -- pediatric-focused safety review of Mydayis and Adzenys ER. I will conclude my presentation with a summary of our findings and conclusions. Next slide, please.

First, we'll start with some background information. Mydayis is a central nervous system stimulant that was approved in the U.S. on June 20th, 2017, submitted by the applicant Takeda, formerly Shire U.S. It's indicated for the treatment of attention deficit hyperactivity disorder, or ADHD, in patients 13 years and older. It's supplied in an extended release capsule at the following doses. Next slide.

Adzenys ER is also a central nervous system stimulant that was originally approved in the U.S. on September 15, 2017. It was manufactured by the applicant Neos Therapeutics. It's indicated for the treatment of ADHD in patients six years and older. It's supplied in extended release oral suspension at a concentration of 1.25 milligrams per ml. Next slide, please.

This pediatric-focused safety review was triggered by pediatric studies completed under the Pediatric Research Equity Act at the time of initial approval. The safety and effectiveness of Mydayis was established in pediatric patients with ADHD ages 13 to 17 years in two placebo-controlled clinical trials with a duration ranging from four to seven weeks. The safety and effectiveness of Mydayis has not been established in pediatric patients at 12 years and younger. The safety and effectiveness of Adzenys ER has been established in pediatric patients with ADHD ages six to 17 in two well-controlled clinical trials with a duration up to four weeks. One study included pediatric patients six to 12 and another included adolescents 13 to 17 years. Next slide, please.

Next, we'll present findings from previous Pediatric Advisory Committee meetings involving amphetamine products. Next slide. OSE, or the Office of Surveillance and Epidemiology, previously evaluated post-marketing adverse event reports with a serious outcome and drug utilization data for extended release

and immediate release Adderall formulation in pediatric patients at the March 2006 PAC. OSE's evaluation identified psychiatric and cardiovascular events as safety concerns for further investigation, which resulted in the eventual labeling of these events.

In April 2018, OSE also evaluated the post-marketing pediatric adverse event reports for two amphetamine products, namely Adzenys XR oral disintegrating tablet and Dyanavel XR amphetamine suspension. No safety concerns were identified at the time. And OSE's recommendation was to continue routine post-marketing surveillance. Next slide.

Next, we will review the relevant safety labeling for Mydayis and Adzenys ER. Next slide. The relevant safety labeling for Mydayis and Adzenys ER products includes the following: a boxed warning describing the high potential for abuse of amphetamine-containing products urging prescribers to assess the risk of abuse and monitor for signs of abuse and dependence while on therapy. The Warning and Precautions section of the labeling includes the

following warnings: serious cardiovascular reactions including sudden death in pediatric patients with structural cardiac abnormalities or other serious heart problems, the importance of monitoring blood pressure and pulse for potential tachycardia and hypertension, psychiatric adverse reactions as amphetamines may cause psychotic and manic symptoms, monitoring height and weight in pediatric patients during treatment because amphetamines are associated with weight loss and the slowing of growth in pediatric patients.

Amphetamines are also associated with peripheral vasculopathy, including Raynaud's phenomenon. Amphetamines may also lower the seizure threshold, and amphetamines may increase the risk of serotonin syndrome when co-administered with agents such as SSRIs and SNRIs. The Adverse Reaction section of the label states that the adverse events in pediatric patients were similar in frequency and type in those seen in adult patients. The most common adverse events being loss of appetite, insomnia, abdominal pain, and decreased weight. The only

difference between the adverse events for Mydayis is categorized in pediatric patients 13 to 17, and Adzenys ER adverse events are categorized by the approval ages of six to 12 and 13 to 17 years. Next slide.

Next, we will present amphetamine product utilization in U.S. pediatric patients. Next slide. Pediatric patients less than 17 years of age that are dispensed an amphetamine prescription decreased from 1.2 million patients in 2006 to 1 million patients in 2018. In 2018, pediatric patients six to 12 years of age accounted for approximately 61 percent or 623,000 patients of the total pediatric patients, followed by pediatric patients 13 to 16 years of age at 38 percent and pediatric patients less than six years of age at 3 percent. Next slide, please.

Next, we'll present post-marketing safety data obtained from the FAERS database. Next slide, please. Adverse events associated with amphetamines or mixed salt of the single-entity amphetamines are not always reported by the trade name of the specific product, for example, Adzenys ER or Mydayis. Therefore, to capture

all adverse events reported with all amphetamines since the previous presentation to the PAC in 2006, we expanded our FAERS search strategy to include all amphetamine products, including Mydayis and Adzenys ER.

Our FAERS search retrieved 1,160 pediatric reports with amphetamines or mixed salts of a single-entity amphetamine product from January 1, 2006 to May 15, 2019. We then screened 1,160 reports and excluded reports from further analysis if they were already labeled and did not look like an apparent increase in severity of labeled events. After exclusion of the labeled adverse events, duplicate reports, transplacental exposure reports describing adverse events unlikely to be related to amphetamine, miscoded and unassessable reports, we identified six pediatric cases of unlabeled, serious adverse events for further review, including two fatal events. Next slide.

We identified two fatal pediatric cases with amphetamines or mixed salt of a single-entity amphetamine. One case reported sudden death due to exertional heat stroke while on amphetamine for ADHD.

In this case, the amphetamine dose or duration of treatment was unknown. Therefore, it's not possible to determine the extent to which the patient's prescribed amphetamine contributed to the development of a fatal heat stroke with the available information.

The second fatal case describes a 13-year-old boy who committed suicide a week after being switched from Vyvanse to Adderall for ADHD after an uncharacteristic aggressive outburst. There was no information provided about the boy's baseline ADHD symptoms, mood, psychosocial milieu, past suicidal ideation, the reason for switching between Vyvanse and Adderall, or a history of evaluation by a health care professional. In both cases, the extent of the causal association with amphetamines was difficult to determine given the available information. Next slide, please.

Next, we present serious unlabeled non-fatal adverse events in pediatric patients. We identified two cases of eye disorders associated with amphetamines. The first case reported six-year-old

Black female who developed glaucoma seven months after starting Adderall XR for ADHD. The second case describes an eight-year-old Caucasian male taking Adderall immediate release and later Adderall extended release for ADHD that developed elevated intraoccular pressure and migraines years after starting therapy with these medications.

We also identified one case describing a vascular adverse event. This case describes a 10-year-old Caucasian female that developed skin vasculitis 10 months after starting dextroamphetamine for ADHD. All these cases reported a long latency. And no additional cases of glaucoma or vasculitis were reported with the use of amphetamines in pediatric patients. Next slide, please.

The remaining serious non-fatal case described acute cervical dystonia in a seven-year-old boy associated with dextroamphetamine withdrawal after the concurrent use of dextroamphetamine and aripiprazole in a child. Dystonia started after the dextroamphetamine withdrawal, and the dystonia resolved after the

dextroamphetamine reintroduction. The case reported a close temporal sequence, and the reintroduction of dextroamphetamine contributing to the resolution of the adverse event supports a possible causal association.

After further investigation, we identified additional cases of acute hyperkinetic movement disorders, including acute dyskinesia and acute dystonia, associated with the concomitant use of other ADHD stimulants including methylphenidate, atomoxetine, and other antipsychotics within the FAERS database and the published literature. This would suggest the pharmacodynamic drug-drug interaction between ADHD stimulants and antipsychotics. Therefore, we classified the safety signal as a newly identified safety signal requiring further evaluation. Next slide, please.

Now, we will transition to describing our evaluation of this newly identified safety signal resulting from this pediatric-focused safety review. Next slide. We performed a search of the FAERS database using the following search criteria. Our

search included ADHD stimulants, including amphetamines, methylphenidate, and atomoxetine. Our antipsychotic lists included both first-generation and second-generation antipsychotics. Because acute dystonic reactions were observed with both antipsychotics and ADHD stimulants, we determined that this is the most likely movement disorder to occur as a result of this wide pharmacodynamic drug-drug interaction. Therefore, we limited our search to reports describing acute hyperkinetic movement disorders. Next slide, please.

We also performed a search of the medical literature using the shown search criteria. Our literature search included the same ADHD stimulants and antipsychotics included in our FAERS search. We used similar terms to capture the acute hyperkinetic movement disorder used in our FAERS search, and we limited our search to English language articles and to case reports in humans. We included all years in our search, which was conducted on January 13, 2020. Next slide, please.

We evaluated all retrieved FAERS reports and published cases using the following case definition, which included the listed inclusion and exclusion criteria. Cases were included if they met at least one of the inclusion criteria, and cases were excluded if they met at least one of the exclusion criteria. Acute hyperkinetic movement disorders were classified as acute dystonic reactions, withdrawal emergent dyskinesia, or unclassifiable mixed movement disorders based on the clinical features and response to treatment. Next slide, please. Because there were multiple permutations of this drug-drug interaction reported, we classified potential drug-drug interactions between ADHD stimulants and antipsychotics using the permutations outlined in the table above.

The main difference between these two classes of medications that are implicated in this drug-drug interaction is that ADHD stimulants cause postsynaptic dopamine receptor or D2 downregulation over time, while antipsychotics cause D2 receptor -- D2 receptor upregulation over time. Therefore, any permutation of

addition, withdrawal, dose change, or switch involving antipsychotics or ADHD stimulants have the potential for resulting in a relative hyperdopaminergic state leading to acute hyperkinetic movement disorders.

This figure illustrates -- next slide, please, sorry. This figure illustrates our selection criteria for the drug-drug interaction cases between ADHD stimulants, atomoxetine, and antipsychotics. After exclusion of duplicate reports, reports describing intentional/accidental overdose or abuse, invalid reports, reports that did not meet the case selection criteria or causality criteria, we identified 36 cases of a potential drug-drug interaction between ADHD stimulants and antipsychotics. Next slide, please.

This table summarizes the selected characteristics of 36 cases associated with the potential drug-drug interaction between ADHD stimulants and antipsychotics. From an ADHD stimulant perspective, 64 percent of the cases were reported with methylphenidate products, followed by amphetamine products accounting for 25 percent of the cases, and

atomoxetine accounting for 4 cases. 94 percent of the cases were reported in children and adolescents.

Compared to adults, children and adolescents experienced extrapyramidal symptoms more frequently. However, acute dystonic reactions are still rare. Most of the cases were reported in males, which corresponds to a diagnosis of ADHD being three to four times more common in males than in females. The cases included in our case series were received from a variety of countries over a period of time. Next slide, please.

53 percent of the cases reported an acute hyperkinetic movement disorder within 24 hours of the drug-drug interaction or the drug change, while 47 percent of the cases reported the movement disorder occurring more than 24 hours but up to seven days after the drug change. 72 percent of the cases had features consistent with acute dystonic reactions, and 19 percent had features of withdrawal emergent dyskinesia. And 8 percent had a mixed movement disorder.

From an antipsychotic perspective, 58 percent of the cases were reported with risperidone, and 27

percent of the cases were reported with aripiprazole. This may be because risperidone and aripiprazole have been studied as adjunctive treatments for disruptive behavioral disorder or conduct disorder. There were isolated cases with other second-generation antipsychotics. However, there were no reports in first-generation antipsychotics, suggesting that they are less frequently used in this population and likely been substituted by second-generation antipsychotics in recent years. The most reported drug-drug permutation involves Scenario 2 representing 20 percent of the cases, which involves the discontinuation of the ADHD stimulant while concomitantly on a second-generation antipsychotic, as well as Scenario 3 which involves the introduction or dose increase of antipsychotic while the patient is on a stable dose of an ADHD stimulant. Next slide, please.

44 percent of the cases reported treatment of an acute hyperkinetic movement disorder with anticholinergics or benzodiazepines, while 47 percent of the cases reported treating the adverse event with

ADHD stimulant and/or antipsychotic withdrawal or dose reduction. And 22 percent of the cases reported treatment of the adverse event with ADHD stimulant and/or antipsychotic initiation or dose increase. In 14 percent of the cases, no treatment information of the adverse event was reported.

It should be noted that more than one treatment modality of the adverse event may have been reported per case. We also show the relevant concomitant CNS medication. They were also reported in some of the cases included in our case series. Next slide, please.

Using our causality assessment criteria we determined the drug event causal association as probable in 11 cases and possible in 25 cases. 50 percent of the cases reported hospitalization as the serious outcome, and one reported a disability. The other cases reported serious outcomes as deemed by the reporter. Next slide, please.

This figure shows the estimated number of patients with a concurrent prescription for an ADHD

stimulant and a second-generation antipsychotic from U.S. outpatient retail pharmacies from 2015 to 2018. The number of patients with a concurrent prescription increased by 33 percent from approximately 1 million patients in 2015 to 1.3 million patients in 2018. Among all patients on any ADHD stimulants, amphetamine products accounted for the majority of patients with concurrent prescriptions with second-generation antipsychotics, followed by methylphenidate and atomoxetine. Next slide, please.

This figure provides the estimated number of pediatric patients with a concurrent prescription for an ADHD stimulant and a second-generation antipsychotic in the outpatient retail pharmacy setting stratified by age. Overall, the number of patients with a concurrent prescription -- with a concurrent prescription appeared to be increasing in all age groups except for adolescents during the examined time period. Next slide, please. This figure shows the estimated number of patients with a concurrent prescription for an ADHD stimulant and a first-generation antipsychotic in the

outpatient retail pharmacy setting. Patients with a concurrent prescription for an ADHD stimulant and a first-generation antipsychotic has increased approximately 29 percent from 58,000 patients in 2015 to 75,000 in 2018. Again, patients with amphetamine products accounted for the majority of patients with concurrent prescriptions with first-generation antipsychotics, followed by methylphenidate and atomoxetine. Next slide, please.

This graph provides the estimated number of pediatric patients with a concurrent prescription for an ADHD stimulant and a first-generation antipsychotic in the outpatient retail pharmacy setting stratified by age. In general, the number of patients with an ADHD -- receiving ADHD stimulant and a first-generation antipsychotic has increased in all age groups. However, low concurrent use was observed in more pediatric patients throughout the study period compared to second-generation antipsychotics. Next slide, please.

Here we discuss the results from our analysis

of these cases. There were no reported drug-drug interaction cases for ADHD stimulant and atomoxetine and first-generation antipsychotics. Most cases reported were reported in children and adolescents suggesting that this population is more sensitive to dopamine changes resulting from this drug-drug interaction. The drug-drug interaction between risperidone and methylphenidate reported the highest number of cases with a probable causality assessment.

We identified a small number of drug-drug interaction cases of amphetamines and second-generation antipsychotic, despite their higher concurrent utilization in the outpatient setting. Risperidone has the strongest binding affinity to D2 receptors among second-generation antipsychotics. Therefore, risperidone's dissociation from D2 receptors is slower, resembling typical antipsychotics and suggesting that this is the most likely second-generation antipsychotic to precipitate this drug-drug interaction with ADHD stimulants. While aripiprazole does not have a distinct pharmacological profile to suggest a higher

potential for this drug-drug interaction with methylphenidate, methylphenidate may also competitively bind to dopamine receptor with a higher potency than amphetamine. Next slide, please.

In conclusion, the totality of the evidence supports a drug-drug interaction between methylphenidate and risperidone. And the evidence was not as strong for the DDI -- for the drug-drug interaction between amphetamine and atomoxetine and other antipsychotics. Next slide, please. In summary -- next slide. FDA will incorporate the drug-drug interaction of acute hyperkinetic movement disorder into all risperidone and methylphenidate product labelings in the Drug-Drug Interaction section. FDA recommends the continued routine monitoring and ongoing post-market safety and monitoring of Mydayis and Adzenys ER.

Thank you for your attention, and I would like to acknowledge the following individuals from across different offices within CDER for their collaboration and contribution to this work. Thank you very much.

DR. WADE: Thank you very much, Dr. Mohamoud, for that excellent presentation. This is Kelly Wade. I'd now like to give a few announcements. One, a reminder to people that when we go to video presentations you will need to make sure your phones are muted and turn up the volume on your computer speakers because any prerecorded videos will only play through your computer speakers. I'd also like to ask members of industry and the press to sign in by sending an email to the PAC at pac@fda.hhs.gov.

COMMITTEE DISCUSSION

DR. WADE: We now have time set aside for clarifying questions yet being mindful that the open public hearing will begin in nine minutes. So we will need to take a pause at that time for the open public hearing. For this session of clarifying questions I would like to ask members of the PAC to use the "raise the hand" button in your Adobe Connect interface. I'd like to start by calling on Dr. Sarah Hoehn for the first clarifying question.

DR. HOEHN: This is Sarah Hoehn. Thank you, Dr. Wade. I had a question for Mo. I don't remember which slide it was, but when you were talking about the football player who had heatstroke and how it was likely unrelated, it just made me wonder, given the tens of thousands of millions of children who are on ADHD meds, if there's any studies or any experience out there about if it interferes with exercise tolerance?

I mean, are there kids who have -- given Adderall and then someone puts them on a treadmill or anything like that? So I just had a general question as to whether or not there's any case studies, evidence, research literature from anywhere out there about amphetamines and exercise tolerance.

DR. MOHAMOUD: Yes. Yeah. This is Mo. Thank you for your question. Yeah. I also share your concern about the exertional heat stroke and the fact that the patient was on amphetamine. I personally am not aware of any research regarding the effect of amphetamines on exercise tolerance. You know, amphetamines are known to increase heart rate and cause

tachycardia, so I guess that has a potential for occurring. But I will see if any of my other FDA colleagues that are on the line that would like to jump in or are maybe aware of any evidence that can perhaps speak to your question a little bit better.

DR. HOEHN: Thank you. I guess I just have a quick follow up question if that's something we should be asking for, given what you said, or if that something we should be suggesting that people look into that at all?

DR. MOHAMOUD: Oh --

DR. CHENG: Hi, this is Carmen from the Division of Pharmacovigilance. When we did this review, there was some initial concern whether we would have additional cases. And we did take a look for any additional cases in FAERS and also the literature case reports, I believe. Is that correct, Mo? Did we do an expanded search?

DR. MOHAMOUD: Yes, yes. We did.

DR. CHENG: Yes. So we did some preliminary exploratory analysis, and it did not seem to be a

signal from this preliminary search.

DR. HOEHN: Thank you.

DR. HAUSMAN: Yeah. Hi, this is Ethan Hausman from Division of Pediatric and Maternal Health. I don't have any prior knowledge on it, but I just did a quick Pubmed search just using some simple terms for "amphetamines" and "exercise intolerance" and "tolerance." There isn't anything that's popping up quickly regarding ADHD. There are about ten articles or so talking about the use of amphetamines for doping, basically, in athletes, but nothing that directly addresses your question.

DR. HOEHN: Thank you.

DR. WADE: Great. Thank you. And thank you to those at the FDA for handling that question. Being mindful of time, I will next call on Randi Oster, recognizing that we will also need to be breaking for the open public hearing, but we at least get the question posed.

MS. OSTER: Yes, thank you. My clarifying question from the first drug presented, the Vyvanse

drug, regarding the three deaths and the dystonia, and in the literature that I read -- the study at Section 5.9 mentioned that there was no absolute safe levels for the interaction of sorbitol, as well as there were no studies done for race. And my question has to do with the fact that literature studies have shown two things. One, that ADHD is a risk factor for being overweight, and the studies done were on children with normal BMI as well as the race -- we had only two Blacks, no Asians, and no Hispanics.

When we look at suicide as an issue, the additional studies that are available is that obesity puts people at risk for suicide. And the second thing is regard to the sorbitol. We know that obese children the studies have shown have an increased usage of sugar free gum as well as diet soda, which contains sorbitol.

So my question that I would like to have clarified is how do we either label -- because there is no labeling on the drug presently that acknowledges sorbitol as an issue with chewing gum or diet soda as well as the fact that we know that one stick of sugar

free gum contains one to two grams of sorbitol. So considering that the safe levels were not studied, I would like to address this and get the comments from the FDA.

DR. WADE: This is Kelly Wade. While we consider who wants to answer that question about the interaction with sorbitol, it is now about to be 11:30. So I'll let someone answer that question when we return from the open public hearing.

MS. OSTER: Thank you.

OPEN PUBLIC HEARING

DR. WADE: I will now open the open public hearing. Both the FDA, Food and Drug Administration and the public believe in a transparent process.

UNIDENTIFIED FEMALE: -- conference. Hello?

DR. WADE: Sorry, I'm just going to read --

UNIDENTIFIED FEMALE: Press 1 to enter the conference. You are joining the meeting. This meeting is being recorded. You have been muted.

DR. WADE: Can you hear me now?

UNIDENTIFIED FEMALE: Yes.

DR. WADE: Great. There was just some interference on the line. A thank you to our audio/visual team for taking care of that. I will begin again.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at this open public hearing session of the Advisory Committee meeting, the 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 the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the

beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationship 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 to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairman. I thank you for your cooperation.

Speaker number 1, your audio will now be connected. Will speaker number 1 introduce yourself? State your name and any organization that you are representing for the record.

DR. ZUCKERMAN: Yes, hi. This is Dr. Diana Zuckerman. Can you hear me?

DR. WADE: Yes. I can hear you.

DR. ZUCKERMAN: Oh, great. Thank you. Wasn't clear. I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research. This National Center is a nonprofit thinktank that focuses on the safety and effectiveness of medical products and consumer products. We don't accept funding from companies that make those products, so I have no known conflicts of interest. Thanks so much for the opportunity to speak today.

My perspective is as a former faculty member and researcher at Vassar, Yale, and Harvard. I'm trained in psychology, epidemiology, and public health. I also have worked at HHS, the U.S. Congress, and the White House. I've spent my career using research funding to improve program, policies, and services to improve public health. I'm also a founding board member of the Alliance for a Stronger FDA, which is a coalition of nonprofit organizations and industry that

lobbies Congress to increase funding so that FDA can do its very important work.

Are you getting a feedback on mine? Is this okay? Can you hear me all right?

DR. WADE: It's fine on my end, Dr. Zuckerman.

DR. ZUCKERMAN: Oh, okay. Great. So today I want to make some general comments about the limits of adverse event reporting and also to express concerns about three of the medical products that are the focus of today's meeting. My general comment is about the adequacy of post-market surveillance. I'm sure you all noticed on several memos the FDA stated something like "the majority of FAERS reports described adverse events that were consistent with the known adverse reactions described in labeling." And when there are fatalities, the memos often explain there's not enough information to determine if the drug or device was primarily responsible, especially since the patients often have "risk factors that may have contributed to the fatal outcome."

So it just seems to me those statements are

really inevitable with FAERS or with MAUDE reports. They usually can't tell us what we really need to know about the risks of medical products, and they certainly can't tell us what parents want to know about the percentage of the likelihood that their child will have these adverse events and how long they'll last. So that's why the FDA has the authority to require post-market clinical trials. They can also use the Sentinel System and other claims data to gather real-world evidence that can supplement that passive, mostly voluntary adverse event reporting. When those additional sources of information are lacking or inadequate, I'm respectfully encouraging you as Advisory Committee members to request that kind of additional information from the FDA. I think I've been struck this morning by the really excellent review of the data that the FDA has, but, unfortunately, those data are so often so inadequate that there's not much possibility of making sense of them.

In terms of the specific products, I want to talk a little bit about Vyvanse for ADHD. I noted, as

you did, that FDA identified a potential safety signal with 23 serious pediatric cases with unlabeled adverse events, including three fatal cases of completed suicides, quite a few suicide attempts and self-injuries, and two acute dystonic reactions. And of course, there's already a movement disorders on the label. But just because movement disorders are on the label doesn't mean that parents are adequately warned.

They don't adequately have the information of how often these happen and how severe they can be. And FDA's been apparently reviewing these, but you're really dealing with a lack of adequate information, which is not the fault of the FDA. But it is the fault of the kind of information that is available.

And just quickly, I'll just mention the second-generation antipsychotics. I participated as a public speaker in these meetings before, and I know there's always been a lot of concern about these second-generation antipsychotics' overuse in children, particularly young children. And I hope that FDA will look into what it can do because these numbers keep

going up. And the fact that they're going up among kids with ADHD I think is particularly problematic.

And the second drug I want to mention is Orencia for juvenile arthritis. The FDA identified angioedema as a safety signal, and so their labeling is being updated. There seems to have been a lot of reports considering that this is a drug that isn't used very often and -- by children. And the one comment I really wanted to make is I was pleased that there's going to be an addition on the label, but that addition is really not expressed very clearly.

I won't bore you with the whole thing, but it's "Concomitant use of TNF antagonists in controlled clinical trials in patients with adult RA, patients receiving concomitant intravenous Orencia and TNF," et cetera, et cetera, et cetera. It goes on and on. It's not till the end of that little statement that it says, "Therefore concurrent therapy with Orencia and TNF antagonists is not recommended." And in fact, it seems to me that statement should be stronger, that it should be a recommended against using both together. So I

just want to encourage that very clear statement in the label so that people will notice it and understand what it means.

And then last, I just want to talk very briefly about the Flourish Pediatric device. The FDA in its memo points out that the post-market data differ from the data that supported this device's approval. The post-market study, however, only had six patients. And only two of them were successfully treated. So we have two issues here.

One is why is the post-market data different? But perhaps more problematic, why are there only six patients in it? And I understand that this is a device not used very often. The total sample is 20 patients. And I think that's really something that I hope that this Advisory Committee will address -- the fact that there's not enough information about this product to know if it's worth using, especially since with the post-market data combined with the premarket data you've got only half of the patients having any kind of success and the fact that only two of the six in the

post-market study were successfully treated.

But despite that, in the memo the FDA says that "the potential benefit of device use to provide a less invasive approach and avoid a major surgical procedure would outweigh the risks." And I would say that's gone a little further than what the data can provide. I think at this point we don't know if the actual benefit does outweigh the risk. It would be wishful thinking to think that it could, and it's true that it might. But we're not there yet. And so I'm concerned that with so few patients, only six in the post-market study and 20 total, it seems to me that it's not appropriate to be making statements about whether this product does have benefits that outweigh the risks.

And so in conclusion I just want to encourage the Advisory Committee. I've been very impressed with the questions asked so far, and my previous experience with this Advisory Committee has been very favorable. But it seems like there's always this default option of the Advisory Committee members raise very important

questions, ask very important questions that need to be answered, and then somehow the result is not much change, not much going on and just keeping on keeping track of adverse event reporting, which is just not good enough to really protect children from products that might not be beneficial and might not have benefits that outweigh the risks or may have very serious risks for a small number of patients. But they haven't been identified as to which patients they are, either in terms of race or obesity or any other issue.

So again, thank you very much for the opportunity to speak. I appreciate it.

DR. WADE: This is Kelly Wade. Thank you, Dr. Zuckerman, for bringing those comments to the open public hearing. Do we have any more speakers today for the open public hearing session? We can proceed with the meeting if we do not have any more open public hearing speakers.

MS. BRILL: Or, Kelly, this is Marieann Brill. If there are any -- if someone would like to speak during the open public hearing session can you please

send us an email at ocoptpacteam@fda.hhs.gov or to my email address marieann.brill@fda.hhs.gov. Thank you.

COMMITTEE DISCUSSION AND VOTE

DR. WADE: This is Kelly Wade. Thank you, Marieann, for providing that email contact. All right. Now I would like to return to our discussion of clarifying question.

DR. McCUNE: Dr Wade, this is Suzie McCune. And I believe that Ms. Oster had asked a question about the interaction with sorbitol, and I wanted to say that we'll be glad to -- what we recognize is that -- and thank her for noting that as an issue. And we'll take that back to the Review Division, as well as our colleagues in OSE, to discuss the interaction with sorbitol and whether it is something that would be primarily a drug-drug interaction on the premarket side or whether it would be something that would be noted as an interaction in the post-market safety evaluation side.

DR. WADE: Kelly Wade. Thank you for that, Suzie. (Inaudible)Dr. Turer for her clarifying question.

DR. TURER: Can you hear me?

DR. WADE: Yes.

DR. TURER: Okay. This is Dr Christy Turer. My clarifying question has to do with the statement that there seems to be a difference in the finding of the dystonia between children and adults. It appears that when the data were presented for children there were much more cases, only two for the adults. But then when the data were presented on the proportions over time of children receiving both stimulants and antipsychotics, comparable data were not presented for adults. And so I'm interested in identifying if we have fewer adults that are both on stimulants and antipsychotics?

I worry about this. In clinical practice, I see kids that come from the community, and it's like the mechanism of those drugs, antipsychotics, make the kids sleepy. The stimulants obviously stimulate them,

and it's almost as if one is being used to treat the side effects of the other.

I don't see that in clinical practice in internal medicine as much. But I would value seeing the data about dual prescription in adults to understand is it truly a difference that kids are more susceptible to dystonia, or is it we don't do that in internal medicine because we really -- we try not to just treat side effects with another drug.

DR. WADE: Thank you for those comments, Dr. Turer. This is Kelly Wade here. There are other raised hands in the Committee. I'm just not sure if someone -- any of the presenters want to speak first?

DR. MOHAMOUD: Hello, this is -- hello, can you hear me?

DR. WADE: Yes.

DR. MOHAMOUD: Yes. Yeah. I would like to share some of the data to answer the question by the PAC member. If we can put up some of the backup slides, please?

MR. BONNER: This will be backup slides for

which presentation?

DR. MOHAMOUD: This is the backup slide for the Mydayis and Adzenys presentation, please.

(Pause)

DR. WADE: Mohamed, can you make sure you introduce yourself? Kelly Wade here.

DR. MOHAMOUD: Yes. This is Mohamed Mohamoud from the Office of Surveillance and Epidemiology, Division of Pharmacovigilance. So the table shown on this slide here shows the estimated number of patients with prescription for ADHD stimulants alone or concurrently with second-generation antipsychotics stratified by drug group and patient age from U.S. outpatient retail pharmacies through 2015-2018 annually. And as you can see, we have the age breakdowns as zero to five, six to 11, 12 to 17, and 18 to 64.

So you were referring to the proportion being different between adults and pediatrics. So it appears that the proportion is quite similar between adults and pediatric groups. If you look across different

pediatric groups zero to five, six to 11, 12 to 17 versus sort of the 18 to 64 group -- because we have it sort of aggregate all adults all together -- so you see the proportionate concomitancy as roughly between 12 to 10 percent despite the proportion being the same. However, we didn't identify as many cases in adults as in kids. So that just gave us sort of the hypothesis that perhaps children are more susceptible to these dopamine changes compared to adults.

Obviously, the limitation being that the FAERS database is spontaneous and passive, so it depends on a reporting by health care professionals, as well as consumers as well as manufacturers. So it's really based on that sort of that voluntary reporting. And obviously, it's also subject to some biases as well -- reporting biases as well.

So that being said, that's what drove us to the conclusion that perhaps children are more sensitive to dopamine changes because sort of the proportion was fairly similar. But yet we didn't see the cases in the -- in post-marketing surveys. Thank you.

DR. TURER: May I ask a follow up clarifying question because when I look at these data, when I'm looking at concurrency of ADHD and SGAs, it actually looks like the proportions for 18 and up are 10 percent concurrent prescriptions? But if you look at zero to five, six to 11, and 12 to 17, it looks like it's 49 percent, 63 percent, and 40 percent. Is that correct? That's a big difference.

DR. MOHAMOUD: I'm sorry. Are you adding between the different age groups?

DR. TURER: No. No. Looking at like in column 1 in 2015 both the concurrency proportion -- well, the concurrent patients in the center row for each year, I'm assuming that's the concurrent patients who are both on ADHD stimulants and on SGAs? Is that correct?

DR. MOHAMOUD: Correct. The middle column, yes.

DR. TURER: And then on the right, concurrency proportion, it looks like for zero to five years down for SGAs the proportion on concurrent SGAs and ADHD

stimulants for zero to five years is 49 percent; for six to 11 it's 63 percent; for 12 to 17, 40 percent; for 18 to 64, 10 percent. So there's a big drop in the adult proportions receiving concurrent ADHD and SGA prescriptions, correct? Am I reading the data incorrectly?

DR. MOHAMOUD: I'm sorry. Can you repeat that one more time?

DR. TURER: Yes. When I look at the concurrency proportion by age -- so even just isolating to year 2015 column -- going down, the concurrent patients in the central column where it says concurrent patients and then associated proportion to the right of that -- particularly when you look at SGAs concurrent with ADHD drugs -- the proportion of zero to five year olds on both of those is 49 percent of the total patient count; for 6 to 11, 63 percent; 12 to 17, 40 percent. But you get to 18 to 65 and it's only 10 percent, suggesting to me there is a big discrepancy by age in concurrent use of ADHD stimulants and SGAs. That was my take in reading this data.

DR. MEHTA: Hi. This is Shek from Drug Use. Are you able to hear me?

DR. WADE: Yeah. Yes.

DR. MEHTA: Yeah. You're reading the data correctly. The proportions are as they're stated. One of the things that is an issue with this particular database that we use in terms of understanding concurrency is that there -- in terms of the claims and events if a patient switches from one agent to another, it's captured as separate events, but the proportions are as you have said. It's that there are a higher proportion of pediatric patients concurrently on SGAs compared to the adult populations as you were stating. Does that answer your question?

DR. TURER: It does. I mean it's concerning to me clinically. I don't know that there's a role of FDA to do anything about that. But I do worry about that because these are children who can't speak for themselves. And if there is an interaction between these drugs and we're using dual agents to treat side effects of each of the drugs, really, given the SGAs

cause profound fatigue, the stimulants cause significant stimulation. Particularly zero to five year olds, they need to be taking at least one nap a day. And they're going to get hyperactive even from sleep deprivation.

So I just -- in terms of clinical practice. I think there needs to be a call for not just treating side effects. And perhaps this is in the domain of like Bridgette Jones and American Academy of Pediatrics, but these data are very concerning to me as a parent, as a pediatrician, and as an internist.

DR. WADE: Kelly Wade. Thank you, Dr. Turer, for highlighting that point. For the next clarifying question I'd like to call on Dr. Jim McGough.

DR. McGOUGH: Yeah. So if I may, I have some questions but --

DR. WADE: Right. Just please state your name.

DR. McGOUGH: Oh. Jim McGough, yes.

DR. WADE: Thank you.

DR. McGOUGH: If I can take a second, so my

main research and clinical expertise is ADHD. And let me just take a second if I can answer these questions. These medicines are not used in combinations to counteract side effects. About a third of the kids with ADHD are extremely aggressive and irritable, and it's common to use an SGA in addition to a stimulant in those kids. That's changing, but that's what that's being used for. This isn't to counteract the sleepiness, et cetera. So this is not treating a side effect with another medicine. That's just not what's going on.

And I think the reason that you see much less of this in adults is that the types of problems that we're treating using these two medicines in kids don't occur in adults. And again, I think it's important as I read the table, whereas 56 percent of the people on SGAs need a stimulant, it's only 11 percent of the kids on stimulants are getting the SGA. And that's within about the third of ADHD children who have this severe impulsivity.

And to the sudden death issue earlier, there's

a basic rate of sudden death amongst youth. You see it. We had a 15-year-old high school kid die here in L.A. last week playing soccer. There are dozens of reports evaluating the exercise effects of the ADHD medicines on sports performance, et cetera. And the risk is really the same risk as recreational athletics, so that's why you get sports physicals for the baseline rate of risk. But it doesn't affect most people. So the data are actually very clear that these medicines don't cause sudden death. That was well looked at about ten years ago. We can talk more about that later.

So my questions on -- just a couple of clarifying points, on the discussion from the Mydayis -- the discussion side for the Mydayis presentation, I might be mistaken, but I have always thought that, whereas both methylphenidate and amphetamine blocks re-uptake of dopamine, it was amphetamine that had more of a direct agonistic effect on the postsynaptic receptor. So if I'm just not reading it right -- but that confused me a little bit. It wasn't my understanding

that methylphenidate balanced postsynaptic receptor. It was more of an amphetamine issue. That's one question.

Secondly, Dr. Strawn may be more of an expert on this, but from my understanding with aripiprazole is that it does have its active state pharmacological profile that depending on the dose can either be a dopamine antagonist or a partial agonist. And I think that actually could give rise to differences with these dystonic sorts of reactions. And the final point -- sorry, I'm choking on a nut.

The final issue where you seem to see this relationship between methylphenidate and risperidone, I wonder how much of that is just incidental and that again, in younger children, I think methylphenidate probably is used more commonly. But more to the point, since risperidone and aripiprazole have indications in autism for irritability, those have been the go-to medicines really for this irritability, aggression seen with ADHD. So I wonder if this relationship you're seeing is just an incident to have these in the most

commonly used combinations, as opposed to, say, some risk that another SGA or even a first-generation agent might have.

So I would not want to misattribute this risk just to these two medicines. It's really, it's just a -- it's the small amount of data that's contributing to this conclusion as opposed to really understanding what's going on. That was it. Did I lose you?

DR. WADE: No. That was excellent. Those are excellent points, and we value your expertise. This is Kelly Wade. I want to make sure that there are no other speakers for the open public hearing. And if there are any speakers for the open public hearing, then we need you to send an email to the PAC so we can make sure we have you on our agenda.

DR. McCUNE: And Dr. Wade, this is Suzie McCune. We're noting that someone has -- one of the participants in the meeting has their hand raised. And that in our minds signified that we thought that there might be someone else that might want to speak in the open public session. And that was why we are

encouraging anyone who has their hand raised in the -- as a participant in the meeting, other than the PAC members or the speakers, to please reach out to the email to give us the information so that we can move you into speaker status. Thank you very much.

DR. WADE: Thank you for that, Suzie. The email address again, if there is someone who is waiting to present at the open public hearing, is ocoptpacteam@fda.hhs.gov. Also, I will remind people we are following the "raise your hand" so I know who to call on. And when you finish with your question, please take your hand down so I know that that has been satisfied. The next clarifying question is Dr. Sayej.

DR. SAYEJ: Hi, everyone. Thank you for the presentations. And I do have a clarifying question for Dr. Kim and a follow up comment to Dr. Zuckerman who spoke in the public time. For Dr. Kim, with regards to the children who either were successful committing suicide or have attempted to commit suicide, do we have any additional information with regard to concomitant mental illness diagnoses and concomitant treatment for

those mental illness disorders? And how long have they been on these ADHD medications before they made the attempts?

It's not very clear. And I understand there are many limitations with the reporting process and the data that can be presented during the reporting process having done that myself in the past when I tried to report cases. There are a lot of limitations in how much information you can put in there. But I'm just curious as to whether we have any idea.

As a gastroenterologist, I do see a ton of patients with ADHD with concomitant mental illness issues including anxiety, depression, bipolar disorders, and oppositional defiant disorders, et cetera. And these -- many patients are on a bunch of medications, including the combination of ADHD and antipsychotic medications. And a lot of these patients do develop a lot of gastrointestinal adverse events mostly from the medications, including anorexia, decreased appetite, weight loss, constipation, abdominal pain -- and a ton of other medications.

Therefore, I end up, in many cases, trying to treat the symptoms rather than identifying that there's an underlying GI disorder. But I'm most of the time I'm treating the symptoms that are caused by some of these medications. So that's a clarification for Dr. Kim.

And my comment to Dr. Zuckerman is that number 1, I thank you and I commend you for coming forward and speaking and raising your concerns. I have been a member on the Pediatric Advisory Committee for about four years. And I have been blown away by the amount of work that the FDA puts in to come up with these presentations and the data that they present this way. Given the limitations, which I completely agree with you that there are a lot of limitations out there, the FDA has always done a tremendous job in identifying some of these new triggers or new adverse events and bringing them forward so that we can analyze them and discuss these new findings.

Having said that, I do think that we have a much bigger problem in this country than the reporting

system. The United States accounts for 5 percent of the world's population, but yet we consume about 75 percent of the world's drug prescriptions. Let that sink in. That is a tremendous number.

Secondly, you know, I have tried to submit adverse event reports and have successfully done so in the past. Unfortunately, many physicians don't have the time and don't necessarily report these adverse events. And I think every one of us is guilty of that. We do our best in terms of reporting some of these adverse events or rare adverse events with certain medications. But the problem with that is there are not many journals that accept case reports anymore.

So there are so many limitations that the FDA has to work with in terms of gathering all of these adverse events and bringing them forward to us and allow us to determine if they're adequate or not and whether they're related or not and whether there's a cause and effect or not. So while I completely agree with your concerns, I think that there are many limitations that we have to overcome as a society and

the cultural effects on our prescription habits in this country and our cultural effects on wanting a quick fix or a magic pill sometimes that -- to treat functional disorders, for example.

So I think this is a long debate and a very complex debate when it comes to these medications which I don't think we will be able to answer today. But again, I thank you and commend you for your comments.

DR. CHENG: Hi. This is Carmen Cheng from Division of Pharmacovigilance in Office of Surveillance and Epidemiology, and I'll be answering for Dr. Kim in her absence. So as far as some of the background medical history, we have the three fatal cases. One did come from the poison database, and the patient had a -- it was very unclear. It said the patient had a history of mental disorder was the exact quote. There was another patient that had a history of conduct disorder. So those are the death cases.

And some of them are unclear how long they've been on the medication. One was intentional overdose. We do not have the length of time that the patient was

on medication. One just restarted after not being on the medication for about 10 to 12 months but had a history of being on the same medication. And then one of the death cases it was actually not known whether the patient was taking the Vyvanse even. It was known that the patient was prescribed the medication, but we don't know whether the patient was compliant either.

And as far as the non-fatal suicidal ideation cases, we had 11 included in our case series. And it really varied in the amount of information that was presented. But when we kind of divide up the 11 cases, we did note that at least five of the cases reported one or more risk factors, and that could include the history of depression, a mood disorder, some kind of stressor going on. Or there were a few patients on antidepressants already. And then one of the patients did report that the event was resolving with counseling and ongoing use of Vyvanse.

And then as far as the other remaining six cases, they did report the resolution of the suicidal ideation or behavior following the discontinuation of

Vyvanse. However, three of these included just a check box without further information and a narrative of the improvement. But all of the six cases were missing some kind of information, whether it's medical history, the concomitant medication, the dose, and time to onset. So it's very complex without the full information to be able to attribute the adverse event in regards to some patients have the background rate or concomitant medication. I hope that answers some of the questions.

DR. SAYEJ: Yes, thank you, and I appreciate the clarification on these patients. Again, this is a proof that the lack of information -- again, this is not necessarily the FDA's fault. It's just the systematic fault that we don't necessarily have all the necessary details or information to allow us to truly make the cause and effect association in some of these cases. So there are a lot of confounding factors here that we can't take into consideration or incorporate into the decision-making process.

DR. WADE: Kelly Wade here. Thank you for

that discussion. The next clarifying question is from Dr. Ron Portman.

DR. PORTMAN: No, Kel, I'm sorry. I don't have a clarifying question.

DR. WADE: Thank you, I'm sorry for that (Inaudible) – Dr. Randy Flick.

DR. FLICK: Hi, Kelly, did I hear you call on me? It's Randy Flick.

DR. WADE: Yes.

DR. FLICK: Oh, great. Thank you and thanks for chairing a challenging meeting. The question I have refers to Dr. Kim's presentation on Vyvanse. If we could go to slide 20. And this is the slide that shows the two cases of acute dystonia, the 26-month-old with accidental ingestion of lisdexamfetamine. And the question I have is one you probably can't answer, but do we have any sense of the order of treatment here?

The child experienced dystonia but received diphenhydramine and lorazepam in the emergency room. Given that diphenhydramine causes or can cause -- not only treat but also can cause acute dystonia, do we

have any understanding of the relationship or the timing of the administration of diphenhydramine in this case?

DR. CHENG: Yes. This is Carmen from Division of Pharmacovigilance. From what I recall on this case that this was -- we don't have the exact order of what was given as the treatment. But this was diphenhydramine and lorazepam were given at -- attempted to be given as a treatment in the emergency room to treat some of these symptoms.

DR. FLICK: Yeah. The question would be did the dystonia appear before or after diphenhydramine? It -- go ahead.

DR. CHENG: Oh, it. It did occur before. It did occur before.

DR. FLICK: Okay. Then that's my question. Thank you.

DR. CHENG: Mm-hmm.

DR. WADE: Kelly Wade. Thank you for clarifying that. The next question will come from Randi Oster. Please remember to state your name at the

beginning.

MS. OSTER: Yes. Thank you. My clarifying question has to go back with the drug Vyvanse. And the question has to go back to the demographics that were studied were children of BMI 26, and again, the race was white -- predominately white with a few were Hispanics. When it comes to suicide, we know that suicidal behavior -- there has been studies. I could give the study across the weight spectrum. The quote is adolescents in excess weight categories are significantly at greater odds of suicidal ideation.

Second, we also know from literature studies that ADHD in boys is a risk factor of being overweight. And third, we know that, again from literature research, Hispanics are 25.8 percent at this age group have a prevalence of being overweight. Therefore, I would like the FDA to comment on perhaps, if we've only studied one level of BMI, perhaps the drug should not be offered to overweight children with the risk, knowing that the second leading cause of death according to Appendix D in the report is suicide. So I

don't know if you've looked at that, but that is a comment that I think we do need to address.

DR. CHENG: This is Carmen from Division of Pharmacovigilance. I will not be able to comment on the clinical -- the preapproval side, unfortunately, on the marketing for the premarketing information. And I don't believe we -- we may have to bring this back to the Review Division.

MS. OSTER: Yes.

DR. McCUNE: This is Suzie McCune from OPT. I want to thank Ms. Oster for the comments. I think that it reflects a difference in what we have seen over the years with respect to trial data and then how to then take that trial data and be able to use it in the context of clinical care. And so we will take the comment back but recognizing that trial data to support a labeling indication can be different from the general population. And that's not just for pediatrics. It's true in general for drug evaluation.

DR. WADE: Kelly Wade. Thank you, Suzie, for that clarifying information and Randi for your

question. Next, we have clarifying questions from Dr. McMillan.

DR. McMILLAN: Yes. This Dr. Gianna McMillan. I wanted to address a previous comment during the public forum that parents rely on physician explanation of side effects. So no matter how complete the labeling is, it comes back always to the physician-patient relationship. Also, the side effects in children have to be reported by parents. So this is one layer of distance from accurate reporting. And then as previously mentioned, physicians don't have the time sometime or the ability to report in a timely manner or completely.

So I would just say that, at the very least, parents need to know how important it is to report. I'm not sure how the FDA or how this Committee would address that. But parents often don't know the kind of questions they should be asking, so they don't know maybe to look for certain side effects. And ideally, they have this complete information from their physician. But that isn't always the case for a

variety of reasons. Like I said, I'm not sure how we can address that with this Committee, but I did want to bring that up.

DR. WADE: Thank you, Dr. McMillan. The next clarifying question -- excuse me. This is Kelly Wade. The next clarifying question is Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: Thank you. This is Roberto Ortiz. I wanted to follow up on an earlier comment with regards to the use of the stimulants and SGAs. And then one other population to consider that may be affected is for the high comorbidity of ADHD patients with bipolar disorder. So it may not be uncommon that direct combination of medications will be required for this population.

I also did a very cursory review of both the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry doctor guidance for the treatment of ADHD. And there are direct comments as to, in complex cases, managing the associated comorbidities. I do not see any indications in either one of the guides as to using the stimulants

specifically for -- or FDA specifically to track -- treat side effects such as insomnia or hyperactivity.

So I don't -- I'm not sure that there is a role for the guides at this point to do anything further based on the existing treatment guidelines. So just wanted to make a comment on that.

DR. WADE: Thank you, Dr. Ortiz, for those comments. This is Kelly Wade. I don't see any further hands raised. So I would just like to ask my own clarifying question if that's okay. I was curious about whether or not the placement of suicidal ideation in the Section 9 Drug Abuse and Dependence is sufficient in that location. That it has been included in the label of Vyvanse? But for children at least, I wasn't sure if that section, Drug Abuse and Dependence, would be reviewed sufficiently for that comment on suicidal ideation to kind of be notable.

DR. CHENG: Hi. This is Carmen Cheng from Division of Pharmacovigilance. Yeah. The location right now is in the Drug Abuse and Dependence, and that's why we really right now consider it unlabeled in

our case series when we review this adverse event, unless it's in the context of drug abuse and dependence. And from the details in the case, they do not appear to be related to drug abuse and dependence. But we do not -- we do not think it needs to be changed at this time due to the lack of evidence of a signal.

Although we have cases reported, we do not also want to alarm others if we don't have sufficient information. So we recommend continuing monitoring for any severe cases that we believe are considered signals and work up -- perform any work ups, if needed, at that time. But right now we are recommending to continue monitoring.

DR. WADE: Thank you for that, Carmen. This is Kelly Wade. The other interesting section of the label that I found in the Vyvanse was Section 5.4 under Psychiatric Adverse Events where there was a nice comment about screening patients for risk factors for developing a manic episode such as comorbid or a history of depressive symptoms or a family history of suicide, bipolar disorder, or depression. And as we

discuss more and more -- or more of these potential for psychiatric adverse events or movement disorders, I was wondering what features -- what highlights adverse events to then be included in the synopsis guidance, the first page of the label, or in the Pretreatment Screening section of a label?

I guess to be clear on that question, what elevates an adverse event to be captured in either the one-page synopsis or in the pretreatment screening? And I understand Dr. Hausman has his hand raised as well.

DR. HAUSMAN: Hi, yeah. This is Ethan Hausman. My hand was raised for the prior question. But it's sort of -- I guess they overlap. And I'm not speaking for the Premarket Review Division right now. This is just the general understanding of how FDA labels.

So if drug X comes in and it's a unique drug that's never been marketed before -- in this case let's say it was the first stimulant medication for the treatment of ADHD -- your controlled trials are

performed. If there's an imbalance in adverse events between a placebo group and a drug-treated group, it's very likely that the adverse events that occur in the drug-treated group could get labeled, whether it's in Section 6 or not as clinically meaningful things -- and I'm using that term very loosely -- or whether it's in Section 5 for more serious issues which you can monitor for or intervene for, or whether it makes it up to a black box -- what we call black box warning. But it's called the boxed warning.

It's an easier lens to look -- it's easier to look at that kind of question when you're looking at a fresh drug when it comes in the first time. When new stimulant medications come on, even though we have a very rich history, they come in and we do controlled clinical trials, crossover studies, placebo-controlled studies, any number of different study designs. And that's a question that's actually more appropriate for the Review Division.

So even though we have a rich history of safety for the entire class of medicines, if a new

stimulant medicine came in and there were in fact an imbalance of suicides, heaven forbid, between the drug-treated group and a placebo-treated group, I want the Advisory Committee to understand that it's very likely that that signal would not get "buried in the label" or put in Section 9. If the drug were in fact approved, it's very likely it would be in Section 6 or Section 5 or even make it up into a boxed warning. That is not because I have any knowledge of any drug program right now where that is an issue. So I want to make that very clear.

On the other hand, if we have drugs that are very old, I guess Dr. Sayej said it's getting more difficult to publish case reports. It's not impossible. Case series are a little bit easier than case reports. And this is not to take anything away from FDA in our review of FAERS, but we have to know that something's occurring.

If we're talking about a drug that's already been approved, we have to be made aware if clinicians or family members or patients notice things. And they

report them either directly to FDA or through their clinicians or from drug companies. And they make it to FDA. We look at that. And while there's the comment that it's getting very difficult to publish a case report, they do make it out.

A well described -- a well characterized case report for the proper issue, whatever that may be, can in fact make it into labeling, not that I have an example that I can tell you about. But we've labeled new safety issues for old drugs based on pharmacovigilance reviews that are done as part of the routine, ongoing portfolio monitoring. It's a robust process that Pharmacovigilance engages in. So just because the drugs are old and just because we've looked at suicidality, whether it was five years ago or a decade ago as a class issue, we had confidence given the data at that time that the issue was appropriately labeled -- but again, given the data that were available at that time.

The other thing I want the Committee to understand is just because we look at something once,

it doesn't mean that we have forever decided that that's a stale issue and it's never looked at again. I'm not bringing up the hint that we should go look at this again right now. I just want to make sure the Advisory Committee understands that just as we looked at something, we may not look at it again a month later. But a decade or so later we do occasionally look at things a second time, particularly if a new study comes out that shows an imbalance that's pretty well characterized between one group and another or if we get a couple of "gold cup case reports." So any number of things can tip FDA over into looking at an issue again. And then, of course, when we do that, it depends on the nature of the data we're looking at.

If a new sponsor comes in and for some reason there's a post-market study commitment that's looked at, we can use information like that to help inform an issue. So I don't have clear answers to any of the questions. I just wanted to take this opportunity to explain the process, particularly for the newer PAC members. So we do look at these things on an

intermittent and ongoing basis. So that's really all I had to say. I just wanted to give a description of how the process works so possibly to help inform your questions or any of the responses from my colleagues. That's it.

DR. WADE: Thank you, Dr. Hausman. This is Kelly Wade. Before we break for lunch, I just want to give one more reminder for the open public hearing. If there was anyone waiting to speak, we just need an email to be sent to the PAC team at the FDA.

We will now break for lunch from 12:30 until 1:00. I want to thank everyone at the FDA and our excellent audio/visual team and members of the PAC for really being flexible and engaged in this call today. And we will return -- we will now take a 30-minute break.

And to panel members, please remember there is no -- there is to be no discussion of the meeting publicly during the break amongst yourselves or with any members of the audience or the FDA. And we will resume at 1:00 p.m. Eastern Standard Time at which

point we will have further Committee discussion and a vote before moving on to our next medication. Thank you, everyone. We'll be back at 1:00.

DR. McCUNE: Dr. Wade, this is Suzie McCune. Before you -- I believe that we need to close out formally the open public hearing.

DR. WADE: Oh. Thank you for that. I missed that text. But at this time we will close the open public hearing and take a 30-minute break for lunch.

[LUNCH BREAK]

COMMITTEE DISCUSSION AND VOTE

DR. WADE: This is Kelly Wade. I want to welcome everyone back, acknowledge everyone's engagement in that great discussion that we had this morning reviewing safety information for the stimulant class medications. I believe that we have covered all the hands raised, and so I would like us to consider transitioning into the voting session. We have three votes today in this stimulant class. Terrific, so this

is the slide of the Committee discussions of both the dystonia and the association of hyperkinetic movement between risperidone and methylphenidate products.

I think the Pediatric Committee today has highlighted and given feedback on the great usefulness of these important safety reviews and noted the high concurrent use of stimulants with the secondary antipsychotic class in particularly young children was striking. And I appreciate this opportunity to have this ongoing discussion today. If I could ask our A/V team to show the Committee Slide 11 of the Vyvanse voting slides.

So the question for the Pediatric Safety Review of Vyvanse or lisdexamfetamine voting: the FDA identified acute dystonia as a potential signal in the pediatric-focused safety review. The subsequent signal review for acute dystonia and ADHD medications did not identify sufficient evidence to support a signal for acute dystonia in ADHD medications at this time. The FDA recommends to continue ongoing post-market safety monitoring.

And we have a few minutes of discussion before the voting will occur. We need to be mindful of our time today. And I remind folks of the Committee that voting will be in response to a question-specific email. So raise your hand if you need or would like to have clarifying information with regard to this question being posed to us today.

It looks like some people are still joining the call, so I want to give us a minute. Again, raise your hand if you need any clarifying information before we transition this Vyvanse question for a vote.

DR. CUNNINGHAM: This is Melody Cunningham. I'm using my phone because it's not allowing me to raise my hand. Should that question have already be --

DR. WADE: Hold on just a minute. Hold on just a minute. This is Kelly Wade. I'd now like to call on Dr. Cunningham for a clarifying question in regards to this question.

DR. CUNNINGHAM: Thank you, yes. This is Melody Cunningham from the University of Tennessee. So my question is simply a logistical one. It is, that

question is not in my email box yet. I wasn't able to raise my hand and ask the question that way. Should it be in the email box already, or will it be sent when it's ready to have us answer it? Because I realize we only have 60 seconds to vote.

MS. BRILL: Hi, Melody, this is Marieann Brill. I am in the process of sending the voting question to everyone right now. Thank you.

DR. WADE: Thank you for that clarifying information. This will be our first time voting through this format, and I welcome our ongoing patience. I think this is actually going to go quite well.

So I will move forward. This is Kelly Wade. If there are no further questions or comments concerning the wording of the question, we will now proceed with the --

DR. CZAJA: Sorry, Kelly. This is Angela Czaja. I raised my hand as well but not sure if it went through.

DR. WADE: Sure, Dr. -- this is Kelly Wade. I

call on Dr. Czaja for clarifying information.

DR. CZAJA: Yeah. I just had a really quick question. I noticed in some of the later questions that the question posed to the Committee used more of the terminology "routine safety monitoring." And I was just wondering if FDA would mind clarifying what exactly would happen when they say, "continue ongoing post-market safety monitoring."

DR. CHENG: This is Carmen Cheng. Sorry, can you repeat your question? I was trying to navigate the A/V system.

DR. CZAJA: Yeah. No worries. I just wanted to maybe clarify a little bit more specifically what actions occur when it recommends continuing ongoing post-market safety monitoring to distinguish it from, I think, later questions that come to the Committee. They use more of the phrase "routine safety monitoring." Is there a distinction?

DR. CHENG: This is Carmen Cheng from Division of Pharmacovigilance. There is no distinction. That is the -- so we plan to continue routine

pharmacovigilance monitoring, which will include ongoing monitoring of the FAERS reports, literature, alerts that we monitor, other databases that we have access to. So this is something that we perform ongoing basis. And if we identify any potential safety signals, any case reports of interest, we will continue to perform any further workups, as necessary.

DR. CZAJA: Thank you.

DR. WADE: Kelly Wade here. There's a clarifying question from Randi Oster.

MS. OSTER: Yes. This is Randi Oster. Can you just explain if you get a majority vote of "no," what does that do?

DR. McCUNE: So this is Suzie McCune. Maybe I can start with this. If we get a majority vote of "no" -- and it's any vote that we get -- what we're going to do is Dr. Wade is going to go through and understand why each of the members voted yes or no. And then we take that information back to the Review Divisions to discuss.

MS. OSTER: So then as that's happening there

is still an ongoing post-market safety monitoring occurring? It doesn't stop the "yes"?

DR. McCUNE: This is Susan McCune. That is correct. And if you have additional information that you would like to add as part of your vote, that would be what Dr. Wade would be asking for you to expound on when she calls on you to tell about your vote.

MS. OSTER: Okay. All right. So a "no" vote means that we'll get to clarify additional information, but it doesn't stop the "yes" vote for it continuing. I appreciate that clarification.

DR. WADE: This is Kelly Wade. Thank you for that useful information. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. If there is no further discussion on the question before us, we will now begin the voting process. You should have received an email from the pediatricadvisorycommittee_vote@fda.hhs.gov with voting instructions.

The instruction is to Reply All to the message and when responding, type your vote "yes," "no," or "abstain" in the body of the email and nothing else. In case you encounter technical difficulties, please email your assigned point of contact or email the ocoptpacteam@fda.hhs.gov. And you may now start voting on Vyvanse. You will have 60 seconds to respond to the voting question.

(Pause)

This is Kelly Wade. I will now close the vote. I am reminded that I will be a timekeeper in the future. Thank you. We will now take a ten-minute break while the FDA compiles the votes. And the vote will then be displayed on the screen. The DFO will read the votes from the screen into the record.

[BREAK]

DR. WADE: This is Kelly Wade. Welcome back. I have heard that the voting slide is completed. I think someone on the audio/visual team can perhaps

share that slide.

It's almost ready. Thank you. So now that the vote is complete, we will go down the meeting roster and have everyone who voted state your name, the vote, and, if you want to, you can state the reason why you voted as you did in the record. And the voting slide is about to be shared. And our DFO Marieann Brill will be reading the vote into the record from the screen.

MS. BRILL: Hello. For the vote -- for the response to the vote -- to the Vyvanse voting question, there are 21 "yes" and one "no." And again, for the record we have 21 "yes" and one "no." Thank you.

DR. WADE: This is Kelly Wade. So let's go down the meeting roster. State your name, your vote, and, if you want, state the reason for why you voted as you did into the record. Starting with Dr. Anne.

DR. ANNE: Hello, this is Premchand Anne. I concur.

DR. CALLAHAN: Dr. David Callahan. I concur and voted yes.

DR. CUNNINGHAM: Melody Cunningham. I concur and voted yes.

DR. CZAJA: Angela Czaja. I voted yes.

DR. DRACKER: Bob Dracker. I voted yes.

DR. FISCHER: Gwen Fischer. I voted yes.

DR. FLICK: Randall Flick. I voted yes.

DR. HAVENS: Peter Havens. I voted yes.

DR. HOEHN: Sarah Hoehn. Sarah Hoehn. I voted yes. And I voted more because I feel like the dystonia is likely related to the mechanism from physiology and not necessarily pharmacology. That was also why.

DR. HOLUBKOV: This is Rich Holubkov. I voted yes based on the presentations and the strength of the data presented.

DR. B. JONES: This is Bridgette Jones. I concur with the FDA's recommendation to continue post marketing surveillance.

DR. O. JONES: This is Olcay Jones. I voted yes. It is for the presentation and trust to FDA. Thank you.

DR. LUKISH: Jeffrey Lukish. I concur. I voted yes.

DR. McGOUGH: Jim McGough. I think the FDA has properly assessed the available data. I voted yes.

DR. McMILLAN: Gigi McMillan. I voted yes.

DR. ORTIZ-AGUAYO: Roberto Ortiz. I voted yes. I concur with the assessment of the available data.

DR. WADE: If we could have -- this is Kelly Wade. If we could have some unmuting for Randi Oster.

MS. OSTER: This is Randi Oster. I voted no. I understand that continuing monitoring would happen anyway, but I want to call to the attention that the demographics do not reflect the population at large who use this drug, as well -- on two areas, the BMI and race. And therefore, I believe additional testing is required.

DR. WADE: Jennifer Plumb, you're next. You may need to unmute.

DR. PLUMB: This is Jen Plumb. I voted yes and concur. I do believe that continued monitoring and

observation for possible indication that further re-evaluation is needed is the appropriate step.

DR. SAYEJ: This is Wael Sayej. I voted yes. I concur with the FDA's statement, and I concur with the previous statements given by my colleagues.

DR. WADE: Jeffrey Strawn, you're next. You may need to unmute.

DR. STRAWN: This is Jeffrey Strawn. I voted yes. I concur. I think that the presentations are consistent and also reflect the known pharmacology of particularly the mixed dopamine-serotonin receptor antagonist, the second-generation antipsychotic.

DR. TURER: This is Christy Turer. I voted yes. I particularly valued Dr. McGough's thoughtful input.

DR. WADE: Benjamin Wilfond, you're next.

DR. WILFOND: Oh yes, yes. Yeah. This is Ben Wilfond. I voted yes.

(Pause)

DR. WADE: Sorry. I was muted that whole time. This is Kelly Wade. I want to thank the members

of the PAC for that voting. We will move on now to the Slide 13, the Mydayis voting slide. I want to remind members of the Committee that we are voting today separately on Mydayis and Adzenys because these are two separate agents. And there are separate emails for voting on these two stimulants.

The Mydayis voting slide reads: The FDA will incorporate DDI, drug-drug interaction, of acute hyperkinetic movement disorder into all risperidone and methylphenidate product labeling in the Drug Interaction section. The FDA recommends continuing routine, ongoing post-market surveillance monitoring of Mydayis. And does the Pediatric Advisory Committee concur? This question is now open to members for clarifying issues or questions about the wording of the question. And I see that Dr. McGough has raised his hand. Dr. McGough.

DR. McGOUGH: Yeah. Thank you. Jim McGough. So kind of two questions -- two and one-half questions. Maybe I'm being too concrete in my reading of the vote question, but Mydayis and Adzenys are both

amphetamines. They're not methylphenidates. So I'm a little confused why the proposal to incorporate the DDI of risperidone methylphenidate is lumped with the questions about Mydayis and Adzenys monitoring since those drugs would not be covered by a new label regarding methylphenidate product. That was question number 1. And again, maybe I'm just confused about how these are worded, but they don't seem logically consistent.

Number two, let me ask a question. Isn't the possibility of acute hyperkinetic movement reactions or disorders already on the label for antipsychotic medication such as risperidone? Anyone who uses these medicines routinely knows that dystonic reactions are a very well-known and described risk. So isn't this already in the label for risperidone?

DR. WADE: Kelly Wade here. Thank you, Dr. McGough, for those clarifying questions. I wonder if Dr. Mohamoud -- Dr. Mo from the FDA could provide some further information?

DR. MOHAMOUD: Yes. This is Mohamed Mohamoud

from Division of Pharmacovigilance Office of Surveillance and Epidemiology. With regards to the first question, yes, this review was initiated by the pediatric labeling of Mydayis and Adzenys ER. However, when we detected the signal, it was initially with dextroamphetamine because we don't really limit our search to just those specific products, Mydayis and Adzenys ER. We expanded the search to include all amphetamine products because we wanted to capture as many reports as possible.

That's when we detected the signal, and we identified additional cases with methylphenidate, as well as atomoxetine and other amphetamine products as well. So that drove us to expand our analysis to include all these drug products in addition to first-generation antipsychotics and second-generation antipsychotics. So that's with regards to the first question. I know it's returning to Mydayis, which is an amphetamine, which is technically not going to be affected by this labeling because the evidence was not strong for amphetamine, but it was stronger for

risperidone and methylphenidate. So that's the response -- I hope that that responds to your first question.

With regards to your second question, yes, dystonic reactions are labeled on the label but not in the context of this drug interaction. We noticed, as the utilization data that was presented during this presentation, so this was concomitant use of these two products, ADHD stimulants and second-generation antidepression or antipsychotics. Therefore, and we noticed the drug interaction occurring when there's a dose adjustment reduce drugs, so the labeling will address this specific drug-drug interaction and its potential contribution to this acute hyperkinetic movement disorder. So I hope that addresses the second question. Thank you.

DR. McGOUGH: Well, it just -- it seems to be a bit like getting pulled over for a broken taillight and then they find something in your car. I mean, it's -- the Mydayis issue alerted you, and then you found something with methylphenidate. Although, these are

all really low numbers, and you've got one case of atomoxetine, which isn't even a stimulant. So I think in general the data here is really a very -- there's a real paucity of data. But again, I think this stuff doesn't seem to make a lot of sense to me. You're talking about methylphenidate. Your problem was with Mydayis. I don't know. It just doesn't seem to hold together.

DR. WADE: Kelly Wade here. I see a hand raised among one of the presenters. Dr. Chen, are there (Inaudible) clarifying information?

DR. CHEN: Yes. This is -- yes. This is Qi Chen from Division of Psychiatry. I also did the review. So for the amphetamine and risperidone, there is only two probable cases. And after a review, we find out other concomitant medication as well as the previously mentioned, like, atomoxetine only have one probable cases. So now the evidence -- the only solid case evidence is only in risperidone combined with methylphenidate have six probable cases.

And as in regards to whether the labeling

mentioned that, it mentioned -- the labeling did mention acute hyperkinetic movement, but it is mainly focused on when we start the medication, risperidone and aripiprazole. So this time we've only focused on the drug interaction, like as Dr. Mo presented in his slides, as multiple combinations, like one add to another, one withdraw from another, and the switch to another one. That is my additional comments.

DR. WADE: Kelly Wade. Thank you very much for that. Dr. Hoehn has a question.

DR. HOEHN: Yeah. This is Sarah Hoehn. This is a follow up to what Dr. -- a little bit related to what Dr. McGough was asking about, I think. So if we're talking about the combination of risperidone and methylphenidate together and that this sort of amplifies something that's already described for them that there's this potential to lead to a dose adjust -- like if you have somebody and then you're adding one of the other medications, you need to dose adjust it.

I guess my question to FDA, or whoever, is whether or not that would merit being a boxed warning?

Because there is a lot of things are potential interaction to everything that's listed there just by the category of medication based on how it works -- but whether or not we are really going to draw that to attention to the provider. And part of it was from something Dr. Zuckerman mentioned during the open session.

Yes, there's 10,000 side effects listed. But if it's really a concern that they need to be modifying a dose when they're adding either methylphenidate to risperidone or vice versa, then should it be something other than just add it the label? Should it be a black box or, again, the question for the FDA is, in similar things when you recommend a very specific dose adjustment, where does that information live?

DR. WADE: Thank you, doctor -- Kelly Wade. Thank you, Dr. Hoehn. Does someone on the FDA side want to respond to that?

DR. MOHAMOUD: Yes. This is Mohamed Mohamoud from the Division of Pharmacovigilance, Office of Surveillance and Epidemiology. The specific

information about the drug-drug interaction with regards to risperidone and methylphenidate only, it is the strongest evidence was for risperidone and methylphenidate. That will be in the Drug Interaction section of the label.

With regards to the second part of the question about it being a boxed warning or anything like that, I think that's reserved for serious adverse events. And in this case the acute dystonia was not deemed to be a serious event warranting inclusion in the boxed warning. So this information about dose adjustment and studying these drugs will be in the Drug Interaction section of the label. I hope that answers the question. Thanks.

DR. HOEHN: Thank you very much. That is super helpful.

DR. WADE: Kelly Wade. The next clarifying question is from Dr. Strawn.

DR. STRAWN: Thank you. This is Jeffrey Strawn. I have three points to consider. First, to me it doesn't appear that the concomitant risk is actually

greater than the risk that would be associated with just a second-generation antipsychotic or mixed dopamine-serotonin receptor antagonist. Second, from my perspective the temporal association of worsening after a dose increase would also be consistent either with withdrawal dyskinesia in the case of a dose decrease or akinesia in the case of a dose increase, both of which are technically classified as hyperkinetic movement disorders. Thus this would not necessarily be a drug interaction.

My third point is that it's possible that with atomoxetine as well as the amphetamine-based products, which are metabolized by cytochrome P450 2D6, as well as with risperidone, which is metabolized through cytochrome P450 2D6, this is simply related to cytochrome P450 2D6 variation. Could someone from the FDA comment on those three points?

DR. WADE: Kelly Wade. Dr. Mohamoud, do you want to address that?

DR. MOHAMOUD: Can you just repeat the first question so we can take it one question at a time?

DR. STRAWN: Sure. So the first question is that it doesn't necessarily appear that the combined risk is actually greater than the risk that would be associated just with a second-generation antipsychotic, in this case risperidone.

DR. MOHAMOUD: Yeah. To be honest with you, I'm not sure how to quantify exactly whether the risk with risperidone alone is higher compared to sort of the combination of both drugs. However, it's well known that acute dystonic reaction occurs with second-generation antipsychotics, and, as you mentioned, it's well described in the label. But what is not well described in the label is this potential pharmacodynamic interaction between the methylphenidate and risperidone. And for that we can -- based on the evidence that was presented during this presentation, we think that this warrants inclusion in the Pharmacodynamic Drug-drug Interaction section within the Drug Interaction section of the risperidone label.

DR. STRAWN: Right. My point in response to that would be that we don't necessarily know that it is

a pharmacodynamic effect. As I mentioned in my third point, it could very easily be a pharmacokinetic fact -- or interaction rather, given that we're dealing with cytochrome P450 and have risperidone, which is a potent inhibitor of 2D6, and also given that we have fairly significant variability within the population there.

DR. MOHAMOUD: Are you referring to risperidone and methylphenidate, or are you referring to risperidone and amphetamines?

DR. STRAWN: Risperidone and amphetamines.

DR. MOHAMOUD: Okay. I was referring to risperidone and methylphenidate specifically. We're not going to label risperidone and amphetamines. That's not being labeled at the moment because the evidence wasn't as strong. But we're labeling risperidone and methylphenidate. And we believe that interaction specifically is a pharmacodynamic drug-drug interaction. Does that make --

DR. STRAWN: And to my second question which was regarding the temporal association of the dose increase or decrease in risperidone, this again could

simply be withdrawal dyskinesia or akinesia, both hyperkinetic movement disorders already associated with risperidone as well as the other second-generation antipsychotics.

DR. CHEN: This is Qi Chen from Division of Psychiatry. So I totally agree with you if we see the scenario is risperidone added to methylphenidate or risperidone withdrawal from methylphenidate, we can maybe it's because of risperidone. But the other scenario so like methylphenidate add to risperidone, or methylphenidate withdrawal from risperidone, we also notice acute hyperkinesia. And also, there are other kind of which ones on another one scenario.

And for your third question, we did have a consultation from the Division of Applied Regulatory Science. And they did do a pharmacokinetic interaction review. And they find out there was no indication that any of methylphenidate, risperidone, or paliperidone would alter the plasma level of the other drugs, which means the methylphenidate and the risperidone doesn't have the pharmacokinetic interaction.

DR. STRAWN: Okay. So this is --

DR. WADE: Kelly Wade. Sorry about that --

DR. McCUNE: Dr. Wade, this is Suzie McCune. I just had a clarifying question or clarifying response about the boxed warning if that would help.

DR. WADE: Go ahead, Suzie.

DR. McCUNE: So in FDA guidance document, just for everyone's information, a boxed warning is ordinarily used to highlight for prescribers one of the following situations: there's an adverse reaction so serious in proportion of the potential benefit from the drug, for example, a fatal, life-threatening, or permanently disabling adverse reaction, that it is essential that it be considered in assessing the risks and benefits of using the drug; or there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug, for example, patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner avoiding use in a specific clinical situation; or FDA

approved the drug with restrictions to ensure safe use. I just wanted you all to be aware of those.

DR. WADE: Kelly Wade. Thank you, Suzie. I think that was really helpful. We have two final questions before we vote. First is from Dr. Turer.

DR. TURER: Thank you. This is Christy Turer. So it seems like the voting question it's -- I think there may have been some confusion. The initial bullet point refers to the DDI of acute hyperkinetic movement disorder into risperidone and methylphenidate. But given Mydayis is an amphetamine, not methylphenidate, it's not being put into the label? So that's my first thing is in terms of clarification.

My second thing is a question about the incorporation of the FDA guidance into the alerting that's occurring through our electronic health records because many of these interactions we'll get alerted about, but there's not a good way outside of us referencing a pharmacologist to understand the actual risk. And so I don't know if there's a way to even grade the evidence and the level of risk. We certainly

have to do that when we put in, like, an allergy to a drug.

But so my question also is about the extent to which the FDA guidance is being communicated or there's any sort of working with electronic health record companies in adjudicating how to address these because it is overwhelming on the alert side. And I think it could be done more meaningfully because, otherwise, it's just -- it's too much as a clinician. But this is one where there was a signal but a small signal and something that you could look at.

And I apologize, one other thought. I've had some patients, older adolescents, young adults -- nicotine can interact with a lot of these drugs, which I didn't realize until I had a patient develop serotonin syndrome. And I'm wondering in our -- in the FAERS database if we have information about tobacco use even whether through vaping or smoking?

DR. WADE: Kelly Wade. Thank you, Dr. Turer. Dr. Mohamoud, do you want to respond to that?

DR. MOHAMOUD: Yes. This is Mohamed Mohamoud,

Division of Pharmacovigilance, Office of Surveillance and Epidemiology. Unfortunately, information about the smoking status of patients is not available through the FDA Adverse Events Reporting System. So it's often not mentioned there. In some cases it is depending on how much detail is provided. But in most cases, the smoking status is not available. Thank you.

DR. WADE: Kelly Wade. Dr. Czaja, do you have a clarifying question regarding this voting slide?

DR. CZAJA: Yes. This is Angela Czaja. This stems a little bit from the discussion that's been happening. And I just wanted to see if you could clarify. When you say you incorporate the drug-drug interaction into a label, could you maybe be a little more specific in terms of what type of detail is included on the label? Is it just a listing of medication pairs, or do you describe a little bit more information based on the evidence that you are basing this labeling change on?

DR. WADE: Kelly Wade. Do you want to respond to that?

DR. MOHAMOUD: Yes. This is Mohamed Mohamoud, Office of -- Division of Pharmacovigilance, Office of Surveillance and Epidemiology. Yes. So there's specific language that we're currently working on that will be incorporated in the drug-drug interaction, in cooperation with the Division of Psychiatry. And we will be as explicit as possible to make this labeling informative. Unfortunately, we don't have the language right now to share with you. But this is just an indication that this language will be included. With further details about what specifically is going to be included, we're still working on that. Thank you.

DR. CZAJA: Thank you. It just sounds like maybe it would be useful based on the some of the concerns raised to be as explicit as possible describing the data as well as the potential scenarios in which the interactions may be occurring. Thank you.

DR. WADE: Kelly Wade. Thank you, Dr. Czaja. Whoever made -- go ahead.

DR. CHEN: This is Qi Chen -- kind of an extra comment. This is Qi Chen, Division of Psychiatry.

DR. WADE: Yes, Dr. Chen.

DR. CHEN: So previously we had, like, a very draft -- a first draft of proposed languages regarding Risperdal. It's kind of like extrapyramidal symptoms could emerge in patients, especially children receiving both Concerta and Risperdal or when adjusting upward or downward the dosage of one or both drugs. So this is a very preliminary draft of the labeling.

DR. WADE: Kelly Wade. Thank you very much for that. That was very useful. The remaining hands that are raised in the box are all people that have been called on. Are there any remaining questions before we move forward with voting?

DR. McGOUGH: Yes, Kelly, it's Jim McGough. I have one more clarifying question.

DR. WADE: Go ahead, Dr. McGough.

DR. McGOUGH: So I had a recollection at a prior meeting of Committee we chose not to support adding something to the label that arose out of off-label practice. And it occurred to me that this risperidone methylphenidate combination, risperidone

(Inaudible) is completely off label. And if you look at the age of the kids getting this, risperidone, I don't believe, has any approval under age 8. So we're adding things to the label that reflect nonlabelled use. And I just wondered if there's a general FDA policy about this? Is it variably enforced? I wonder if we open Pandora's box by putting things on the label that apply to off-label usage.

DR. McCUNE: So Dr. Wade, this is Suzie McCune.

DR. WADE: Go ahead.

DR. McCUNE: So Dr. McGough, thank you for your very insightful comments. And I think that this is important information that the Review Division -- and you've heard that both the Review Division and the Office of Surveillance and Epidemiology are on the call today -- can take back to further discussions within the Agency.

DR. WADE: Kelly Wade. Thank you, both Dr. McGough and Suzie, for that discussion. I'm confident that information will be taken back. If there are no

further questions or comments concerning the wording of the question for Mydayis, we will now proceed with the question and open -- oh, sorry. Excuse me. If there's no further discussion on this question, we will now begin the voting process. Again, this is a separate email for Mydayis. And if you have previously voted, you need to do it again. We want to make sure we've got the clear vote after this discussion.

We will now begin voting. You should have received an email from pediatricadvisory_vote with voting instructions. The instruction is to Reply All to the message. When responding, type your vote "yes," "no," or "abstain" in the body of the email and nothing else. In case you encounter technical difficulties, please email your point of contact or the email ocoptpacteam. Please start voting only on Mydayis. You will have 60 seconds.

(Pause)

That completes the 60 seconds. We will now take a ten-minute break while the FDA compiles the votes. The votes will then be displayed on the screen,

and the DFO will read the vote from the screen into the record. Thank you.

[BREAK]

DR. WADE: Kelly Wade. Thank you, everyone, for your patience. The votes are ready and are now shown on the screen. The DFO Marieann Brill will now read the votes from the screen into the record.

MS. BRILL: Hello. For the record, the Mydayis voting results are as follows. There are 20 "yes" and two "no." Again, there are 20 "yes," two "no." Thank you.

DR. WADE: Thank you. This is Kelly Wade. We will now go down the list. State your name and your vote and, if you wish, any reasons or clarifications for your vote, starting with Dr. Anne.

DR. ANNE: This is Premchand Anne. I agree with the FDA's recommendation.

DR. CALLAHAN: This is David Callahan. I vote yes.

DR. CUNNINGHAM: This is Melody Cunningham. I also vote yes and concur with the conclusions of the FDA.

DR. CZAJA: This is Angela Czaja. I have voted yes because, while I understand that there may be other mechanisms underlying some of the observations seen, I thought it was important to highlight this potential interaction for the clinicians and families.

DR. DRACKER: Hello. This is Bob Dracker. I voted yes. And I just wanted to comment that I treat a number of children with risperidone, particularly autistic children, some of which are also on stimulants like methylphenidate. And to be honest with you because I follow what I considered to be minimal effective dosing guidelines and only using as much as I need to, I don't think I've seen a child with a reaction or any movement disorder in over five years now. So I have felt very comfortable with both. But obviously, I'm always watching them for any child on risperidone. Thank you.

DR. FISCHER: This is Gwen Fischer. I voted

yes for the same reasons that Dr. Czaja stated.

DR. FLICK: Randall Flick. I voted yes.

DR. HAVENS: Peter Havens. I voted yes.

DR. HOEHN: Sarah Hoehn. I voted yes.

DR. HOLUBKOV: Rich Holubkov. I voted yes.

DR. B. JONES: Bridgette Jones. I voted yes.

DR. O. JONES: Olcay Jones. I voted yes.

DR. LUKISH: Jeff Lukish. I voted yes.

DR. McGOUGH: Jim McGough. I voted no. I think really I don't think the data here hold any water. You've six cases of who knows what quality but a denominator of millions of prescriptions for an adverse event that is actually, should it occur, it's pretty easily managed. I mean, I don't think there's a signal there.

Also, I think there's difficulties. It's not too hard to propose what mechanism is underlying this. Dystonic reactions occur when there's a relative decrease of dopaminergic transmission compared to some other neurotransmitters. And I think in the excretion phase of the stimulant, you basically are creating a

system where suddenly dopamine transmission -- dopamine signaling is falling. And that could certainly lead to a reaction. And possibly, since methylphenidate has a steeper excretion curve compared to amphetamine, maybe there's a little bit more of a risk with that.

But if it's going to occur, these side effects could occur with any stimulant with any neuroleptic. I don't think there's any justification, really, for picking on methylphenidate-risperidone. Probably their presence in your database reflect the fact they're the most commonly used medicines. But I think it's naïve to think, if this is a risk worth noting, that it doesn't apply to the other compounds as well.

But I think the bottom line is this is such a small, small occurrence that you really don't have anything here. So I would not change the labeling. Although, as I said, the labeling is already there for kinetic difficulties with all the neuroleptics. That's there, and anybody prescribing these medicines should anticipate the possibility of an adverse event such as in a dystonic reaction. So I vote no.

DR. McMILLAN: Gigi McMillan. I vote yes.

DR. ORTIZ-AGUAYO: Robert Ortiz. I vote yes.

MS. OSTER: Randi Oster. I vote yes.

DR. PLUMB: Jen Plumb. I vote yes. And I think coming from an emergency department setting where we are exposed to so many potential causes of any one condition presenting to us, having this be labeled in the literature for us and for the pharmacists that we work with I think is potentially quite helpful because those of us that aren't prescribing these medications every day but are potentially treating those with side effects of them benefit from the heads up.

DR. SAYEJ: This is Dr. Wael Sayej. I voted yes, and I concur with my colleague's statements.

DR. WADE: Kelly Wade. Next up is Jeffrey Strawn. You might be muted.

DR. STRAWN: I'm sorry about the muting. This is Jeffrey Strawn. I voted no. Briefly, I think that this is based on fewer than a half dozen reports, as well as the elimination point that was recently raised by Dr. McGough in his comment. I feel that there's

insufficient data to suggest that there's an increased risk of an interaction. Also, I think that the pharmacodynamic mechanism, while certainly plausible, is very speculative, particularly in light of the fact that there are many similar pharmacodynamic interactions that exist with other even over-the-counter medications wherein we haven't observed this signal.

DR. TURER: This is Christy Turer. I voted yes.

DR. WILFOND: This is Ben Wilfond. I voted yes.

DR. WADE: This is Kelly Wade. Thank you very much. I think that was very valuable comments that the Committee provided. We will now move forward to Adzenys ER. I'd like to ask that slides -- that we display Slide 15, the Adzenys ER voting slide.

It is very similar, as you will see Adzenys ER voting slide. The FDA will incorporate the drug-drug interaction of acute hyperkinetic movement disorder into all risperidone and methylphenidate product

labeling in the Drug Interaction section. The FDA recommends continuing routine, ongoing post-market safety monitoring of Adzenys ER. Does the Pediatric Advisory Committee concur?

And I would just note that although we reviewed these drugs together in Dr. Mohamoud's presentation, we do need to vote on these separately. I would also like to take this time to remind the public observers that, while this meeting is open for public observers, public attendees may not participate, except at the specific request of the panel. Are there any issues or questions about the wording of this question? Raise your hand if you would like to be called upon. And given the similarities between this question voting slide and the one that we just reviewed for Mydayis, there may not be as much discussion.

If there is no further discussion on this question, then we will now begin the voting process. You should have received an email from the pediatricadvisorycommittee_vote with voting instructions. The instruction is to Reply All to the

message, and when responding, type your vote "yes," "no," or "abstain" in the body of the email and nothing else. In case you encounter technical difficulties, please email your assigned point of contact or email the ocoptpacteam. Please start your voting on the Adzenys ER email response, and you will have 60 seconds to respond to the voting question.

(Pause)

I believe our 60 seconds are up. So everyone should have voted, and this will close the voting session.

(Pause)

This is Kelly Wade. Again, as before we will be in a ten-minute break while the FDA compiles the votes. The votes will then be displayed on the screen, and the DFO will read the vote from the screen into the record.

[BREAK]

DR. WADE: This is Kelly Wade. Thank you to

everyone for their patience and the work of all the staff behind the scenes. The vote is complete. It is projected here on the slides. And I will ask our -- Marieann Brill to read the vote from the screen into the record.

MS. BRILL: Hello. Hi. For the voting results for Adzenys ER for the record there are 21 "yes" and two "no." Thank you.

DR. WADE: Thank you. We will now 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. We will start with Dr. Anne.

DR. ANNE: Premchand Anne. I voted yes.

DR. CALLAHAN: David Callahan. I voted yes.

DR. CUNNINGHAM: Melody Cunningham. I voted yes.

DR. CZAJA: Angela Czaja. I voted yes.

DR. DRACKER: Bob Dracker. I voted yes.

DR. FISCHER: Gwen Fischer. I voted yes.

DR. FLICK: Randall Flick. I voted yes.

DR. HAVENS: Peter Havens. I voted yes.

DR. HOEHN: Sarah Hoehn. I voted yes.

DR. HOLUBKOV: Rich Holubkov. I voted yes.

DR. B. JONES: Bridgette Jones. I voted yes.

DR. O. JONES: Olcay Jones. I voted yes.

DR. LUKISH: Jeffrey Lukish. I voted yes.

DR. McGOUGH: Jim McGough. I voted no. Same reasons as with Mydayis. I don't see that there are any data here.

DR. McMILLAN: Gigi McMillan. I voted yes.

DR. WADE: Kelly Wade. Dr. Ortiz, your vote is next. You may be on mute.

DR. ORTIZ-AGUAYO: Roberto Ortiz. I voted yes.

MS. OSTER: Randi Oster. I voted yes.

DR. PLUMB: Jen Plumb. I also voted yes. And again from an acute care and emergency department setting, I do think it is important to have these labels as potential effects for those of us to be able to pull that out of the data and literature.

DR. SAYEJ: Wael Sayej. I voted yes.

DR. STRAWN: Jeffrey Strawn. I voted no. I refer to the reasons that I stated earlier.

DR. TURER: Christy Turer. I voted yes.

DR. WILFOND: Ben Wilfond. I voted yes.

MS. BRILL: Hi, Kelly. This is Marieann Brill. I would like to correct the number of votes. So technically there should be 20 "yes" and 2 "no." We counted one of the SGEs twice. So there should only be 20 "yes" and 2 "no." Thank you.

(Pause)

DR. McCUNE: Dr. Wade, this is Suzie McCune. Are you on mute? Perhaps --

DR. WADE: I am on mute. Thank you so much. I would like -- this is Kelly Wade. I want to -- I just was thanking people silently for their engaging discussion and votes. I recognize we are running about 55 minutes behind, and we were due for a break at 2:45. And so we can either go through Orencia, or we can take a short five-minute break. Are there strong opinions on that?

DR. HOEHN: I vote to forge ahead. This is

Sarah Hoehn.

DR. WADE: Great. I see another vote in the chat as well, so let's forge ahead. And we will take a shorter break than previously planned between Orencia and Gamunex. So I just want to get in my right place.

CDER: STANDARD REVIEW OF ADVERSE EVENT PRESENTATION CONT'D

ORENCIA (ABATACEPT)

DR. WADE: Okay. We will now proceed with the presentation from the FDA on Orencia. We are going to do this in the live presentation mode given the difficulties we had in the video presentation before.

DR. HARINSTEIN: Great. This is Lisa Harinstein. Can everyone hear me okay?

DR. WADE: Yes. Thank you.

DR. HARINSTEIN: Great. Thank you. Again, my name is Lisa Harinstein. I'm a Team Leader in the Division of Pharmacovigilance, and today I'll be discussing a pediatric-focused safety review for

abatacept. This presentation will consist of the following sections, and we will start with the background information.

Abatacept is an immunosuppressant agent approved by the FDA in December of 2005 for the treatment of adult rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, or PJIA, and adult psoriatic arthritis. There we go. Sorry about that. Abatacept may be administered as an intravenous infusion or as a subcutaneous injection.

After abatacept's approval in 2005, its indication for the intravenous formulation was expanded in April of 2008 to include PJIA for ages six years and older. This labeling change was implemented in accordance with the Pediatric Research Equity Act, or PREA. And due to this pediatric indication expansion, a pediatric-focused safety review was completed for the September 2009 Pediatric Advisory Committee meeting. The safety review did not identify any new safety concerns for abatacept use in the pediatric setting, and routine monitoring was recommended at that time.

In March of 2017, abatacept indication was then expanded to include PJIA for ages two years and older for the subcutaneous formulation. This PREA labeling change prompted the current review and today's discussion. It was supported by an open-label study evaluating the pharmacokinetics, efficacy, and safety of subcutaneous abatacept in pediatric patients.

We will now move on to the relevant pediatric labeling. Abatacept label contains the following warnings and precautions listed here for your reference. Notably, adverse reactions in pediatric patients derived from clinical trials have been similar in frequency and type to those observed in adults. As you can see on this slide, the most frequent adverse reactions were reported in PJIA patients treated with the IV formulation included infection, and upper respiratory tract infections and nasopharyngitis were most common. Additionally, other adverse reactions included headache, nausea, diarrhea, cough, pyrexia, and abdominal pain. Pediatric patients treated with subcutaneous abatacept experienced a similar adverse

event profile as pediatric patients treated with the IV formulation with the exception that local injection site reactions were reported with the subcutaneous formulation.

To complete our pediatric-focused safety evaluation the Office of Surveillance and Epidemiology investigated drug use trends with abatacept. We examined the annual number of patients who had a prescription or medical claim for abatacept based on a sample of U.S. pharmacies, clinics, hospitals, and physician offices. The data showed that abatacept utilization in patients younger than 18 years of age was low. In 2018, pediatric patients accounted for 2 percent of a total of about 37,000 patients who had a prescription or medical claim in the U.S. for abatacept within our sample. Of the pediatric patients who did receive abatacept, the majority, or 72 percent, of pediatric patients were adolescents age 12 to less than 18 years of age.

We will now discuss the adverse event analysis. To conduct our analysis we searched the FDA

Adverse Event Reporting System, or FAERS, database for all pediatric reports coded with a serious outcome between July 7, 2009 to December 18, 2019. Because a previous abatacept pediatric safety review included data through July 7, 2009 we used this date as a start date for the current analysis. After exclusion of duplicates, unlikely or unassessable reports, reports describing labeled adverse events, and other reports not describing adverse events with abatacept in pediatric patients, two pediatric cases of unlabeled serious adverse events were identified for further review. The two serious unlabeled adverse events were inflammatory bowel disease and angioedema.

With respect to the inflammatory bowel disease signal, we identified a case of an 11-year-old female patient who developed colitis approximately six months after starting abatacept. She received concomitant leflunomide, which is labeled for colitis in the Adverse Reaction Post-Marketing Experience section of the leflunomide product label. Therefore, this single report did not constitute a safety signal due to the

presence of a potential alternative cause, which was the concomitant leflunomide, and limited information within the case.

With respect to the angioedema signal we identified a case of a 16-year-old female who was treated with her fifth dose of intravenous abatacept for spondylarthritis who developed angioedema. This signal led to a full safety review of 83 cases in both pediatric and adult patients. And of note, the single pediatric case that we just discussed was the only pediatric case in this review, and so there were 82 cases in adults. This review led to a safety labeling change, which was approved on June 17, 2020, to include angioedema and information about this signal within the Warnings and Precautions Section 5.2 Hypersensitivity of the abatacept product label.

Next, I will summarize the finding from our evaluation. In summary, our pediatric assessment identified angioedema as a potential signal, which was assessed in a separate concurrent signal review and resulting in a safety labeling change of June of 2020.

Pediatric use of abatacept is low based on drug use data with only about 2 percent of abatacept use being reported in patients less than 18 years of age in 2018. The pediatric reported adverse events are consistent with known adverse events described in abatacept labeling. The FDA recommends to continue ongoing, post-marketing safety monitoring. Does the Pediatric Advisory Committee concur?

I'd like to acknowledge those who are listed on this slide for their contributions to the review and the presentation today. And that concludes my presentation. Thank you.

COMMITTEE DISCUSSION AND VOTE

DR. WADE: Kelly Wade. Thank you very much for that review of abatacept, otherwise known as Orencia. As we move forward with clarifying questions let's go ahead and display Slide 18, the Orencia voting slide. And we will now proceed with taking clarifying questions for the presenter. Remember to raise your hand so that I may call on you by name. When called

on, please state your name for the record before you speak. And if you can, please direct the specific question to the specific presenter. We can begin with Dr. Turer.

DR. TURER: Hi. This is a pretty rapid question. Angioedema is very common in using ibuprofen and other NSAIDs, and we know many patients with rheumatologic conditions will take those even over the counter. Do you have information on the case report whether the patient may have been taking any ibuprofen or over the counter NSAIDs and/or, like, an ACE inhibitor, which also is known to cause angioedema?

DR. HARINSTEIN: This is Lisa Harinstein in the Division of Pharmacovigilance. Thank you for that question. So in that case, the patient was prescribed as-needed ibuprofen, but there was no evidence in the case that the patient had taken ibuprofen prior to the onset of the angioedema. Within our case series of the 83 cases overall, we did characterize patients who received other products that may be associated with angioedema, but we did include that information in our

over causality assessment. And so if we thought that was more likely that that agent was associated with the angioedema or we could not rule it out, we actually excluded that case from our overall case series.

DR. TURER: May I ask one related follow up question?

DR. WADE: Go ahead, Dr. Turer.

DR. TURER: Is it known what the race/ethnicity of the patient was? We tend to see angioedema more in African American patients.

DR. HARINSTEIN: This is Lisa Harinstein again from the Division of Pharmacovigilance. Let me just pull up the full case and double check, but I do not believe I have that information. But give me one second.

(Pause)

I do not have that information.

DR. WADE: Kelly Wade. Dr. Dracker, do you have a clarifying question?

DR. DRACKER: I do. Bob Dracker. Was there a delay in the adult patients who experienced angioedema

like there was in the pediatric case?

DR. HARINSTEIN: Yes. This is Lisa Harinstein again in the Division of Pharmacovigilance. There were cases of delayed-onset angioedema occurring in adult patients, and I can get the overall statistics if you would like to see it. It's in some of my backup slides. If we're able to get those, I can show you the descriptive characteristics. So we did -- oh, yep?

DR. DRACKER: But the majority of -- go ahead. I'm sorry.

DR. HARINSTEIN: Oh. So I was going to comment that we did include information about immediate onset and delayed onset of the angioedema within the labeling so that way clinicians are aware that this has occurred.

DR. DRACKER: In the adult cases, were most of them immediate?

DR. HARINSTEIN: I'd have to look up that information. If you give me a second, I can pull it up.

DR. DRACKER: Okay.

DR. HARINSTEIN: Are we able to pull up the backup slides? It would be Slides 37, 36. It would actually be Slide 36, please.

So this is Lisa Harinstein again in the Division of Pharmacovigilance. This slide shows the descriptive characteristics of the angioedema case series with abatacept. And there were 83 total cases. And again, 82 were in adults and one in a pediatric patient. As you can see in the top row, the time to onset of angioedema from the most recent abatacept exposure is provided there. And you can see delayed onset, which was defined as greater than or equal to 24 hours or greater than or equal to one day from administration of abatacept, would occur in about 31.3 percent of the cohort, so about a third of patients.

DR. DRACKER: Okay.

DR. WADE: This is Kelly Wade. Our next clarifying question comes from Bridgette Jones.

DR. B. JONES: Yes. This is Bridgette Jones. I just find it really interesting that this case series was triggered by the pediatric event -- that one

pediatric event that was reported. Can the FDA describe the post-marketing surveillance activity toward the adult indication and maybe some of the reasons why this potential safety signal wasn't picked up prior in adult study?

DR. HARINSTEIN: Hi, this is Lisa Harinstein again in the Division of Pharmacovigilance. Thank you for that question. So the FDA receives over 1 million spontaneous adverse event reports on an annual basis. Therefore, we have to use a risk-based approach to identify signals. And we use various data sources for this such as screening through FAERS reports, data mining, or using signal disproportionality, and screening through literature. Additionally, we write different types of reviews, some of which have the potential to identify signals through a systematic review of data such as the pediatric reviews that we're discussing today. I mean, we use these tools together to identify signals because they provide different information.

So specifically for angioedema at the time,

there was -- the signals of disproportionality did not signal that there was actually a signal there. And so actually doing this pediatric review worked out perfectly and with the purpose of doing this review to identify signals. So this is just one tool that we have to help us identify a signal.

And so that is why it wasn't basically identified earlier is because there wasn't a signal disproportionality. But we do review adverse event reports that are reported to FAERS on a weekly basis, so the new adverse event reports get reviewed. So we are still monitoring for this signal as well to make sure that there's no new reports that would signal that there needs to be a change in labeling again or anything else that would need to be taken on.

DR. B. JONES: Thank you.

DR. WADE: Kelly Wade. The next clarifying question comes from Randi Oster. We'll need to unmute her phone.

MS. OSTER: Yes. Okay. Thank you. Just a clarifying question on the actual question. It was

identified and added to the label in June of 2020. Is the question that we're going to be adding this to the label for pediatrics as well, or is it, once it's there, it's on all the labels?

DR. HARINSTEIN: This is Lisa Harinstein again in the Division of Pharmacovigilance. So I believe the question is just to continue ongoing post-marketing safety monitoring. Because angioedema is already added to the label, I don't believe that we will be voting on that specifically. But anyone from OPT, if there's something that you believe is different, feel free to chime in.

DR. McCUNE: So this is Suzie McCune from OPT. Thank you, Lisa. I agree that this is a notification that angioedema was added to the label for safety issue and there wouldn't be a separate pediatric versus adult safety note in the label. But it is to provide you the information that based on the review, angioedema was added to the labeling in June of 2020. And that what we are asking you to vote on today is based on the pediatric safety evaluation for this product, do you

agree with ongoing post-marketing safety monitoring?

MS. OSTER: I understand. Thank you.

DR. WADE: Kelly Wade. And there's just a data question from Dr. (Inaudible).

DR. McCUNE: Kelly, this is Suzie. I think we may have lost you again.

DR. WADE: Oh, really? Huh. I'm not muted.

DR. McCUNE: You just faded a little.

DR. WADE: Oh, okay. Sorry. There is a question from Dr. Turer just about the data ensuring that because abatacept is an (Inaudible) and most of the data comes from retail pharmacies rather than children's hospitals, could we be missing data on children for receiving abatacept infusions?

DR. HARINSTEIN: Hi, this is Lisa Harinstein in the Division of Pharmacovigilance. So just to clarify that question, are you concerned that we're missing data with respect to drug utilization?

DR. TURER: Correct. I would expect -- and this is Christy Turer. I would expect that reported adverse events would occur just about anywhere. But in

terms of the prescriptions, I guess it's a clarifying question regarding any differences in the quality of the data, both in -- because we're -- the question that we need to vote on is ongoing monitoring and post-marketing safety monitoring. But recognizing that FAERS does not -- well, maybe FAERS does. But our reporting on the prescription utilization of drugs doesn't include children's hospitals prescriptions. This is an infusion and very likely is being given at children's hospitals.

DR. HARINSTEIN: So this is Lisa Harinstein again in the Division of Pharmacovigilance. I would have to refer to Drug Use to answer this question since it deals with the utilization data. But with respect to adverse events being seen in the children's hospital, this would be like any other person reporting to MedWatch and -- for being -- reporting adverse events. So it's spontaneous and voluntary, so they can report, but it's not mandatory for them. So we may not receive all reports which is just a limitation over all the spontaneous adverse event reports. But Drug Use,

if you could answer the other portion of the question?

DR. PHAM: This is Tracy Pham from Drug Use, in the Office of Surveillance and Epidemiology. So in our analysis, we basically look at a sample of the number of patients who have a prescription or a medical claim from a sample of, like, physician offices, hospitals, pharmacy, so it might not be representative of all the use in the U.S. But we do capture a -- I think we have about -- the sample will contain about 2,534 clinics, hospitals, physician offices in the U.S. and about 8,000 pharmacy, such as retail and mail-order specialty. Does that answer your question?

DR. TURER: I am not sure. This is Christy Turer. I want to understand if we have the right denominator for use when looking at adverse events in terms of prescriptions dispensed.

DR. PHAM: So this is Tracy from the Office of Surveillance and Epidemiology. So this is looking at the number of patients. We didn't analyze it -- the number of prescriptions that were dispensed for abatacept. So this is the number of patients who had

either a prescription or a medical claim from a sample of patients that we looked at in the database.

DR. TURER: This is Christy Turer. So that answers the question. So ideally, the claims data would fill in the gap of any data missing from children's hospitals?

DR. O. JONES: Dr. Wade, this is Olcay Jones. I believe that you allowed me to speak for a second in the chat? I would like to --

DR. WADE: Yes. Hold on a second. I just want to make sure -- Dr. Turer, I think your question was satisfied. Is that true?

DR. TURER: This is Christy Turer, yes.

DR. WADE: Great. Then yes, Dr. Jones, you are next. Sorry. This is Kelly Wade, and I'm calling on Dr. Olcay Jones for the next clarifying question.

DR. O. JONES: Yeah. Oh, thank you. This is -- I would like to ask if there is more information on the underlying diagnoses or the age of these patients, mean age, or it is -- versus the first, early onset, late onset, the details, and is that available?

DR. WADE: Kelly Wade. Is the question, Dr. Jones, about the -- primarily the adult patients?

DR. O. JONES: Yes. Primarily the adult patients.

DR. WADE: Okay.

DR. HARINSTEIN: This is Lisa Harinstein, the Division of Pharmacovigilance. So are you interested in the information about the patients who had angioedema or just overall --

DR. O. JONES: Right. With -- correct, in your cohort, yes.

DR. HARINSTEIN: Yeah. So if we could refer to backup Slide 35, please? Great. Oh. There we go. So again, this slide shows the descriptive characteristics of the angioedema case series of abatacept. And again, 82 patients were adults, and one was a pediatric patient. You can see here that the median age was 59. 71 of 83 had the age reported.

And then as far as the abatacept indication, you can see it varied, but the majority had rheumatoid arthritis, followed by arthritis, and

spondyloarthritis, arthralgia, and then about 20 percent did not report the indication. You can see the years that these reports were received by the FDA. And about 75 percent or so were United States reports, and then about a quarter were reported from foreign countries. If you could go to the next slide, please?

We already went through the time to onset. And then as you can see about 65 percent had a serious outcome of which 14 resulted in hospitalization. And we deemed about 20 percent to be probable causality assessment and then about 80 percent to be possibly associated with abatacept.

DR. O. JONES: Thank you. So the majority of the patients probably using Orencia is with rheumatoid arthritis. Do you have a proportion of that -- do you have a correction factor about Orencia arthritis patients have -- more inclined to develop angioedema versus is this correlating with the denominator or not? I think that's what I'm trying to ask.

DR. HARINSTEIN: So this is Lisa Harinstein again in the Division of Pharmacovigilance. So we did

not have the drug use data by indication, so I'm not clear as to what the, I guess, denominator of the rheumatoid arthritis patients would be. I also am not aware, necessarily, of a correlation between the rheumatoid arthritis and angioedema, other than someone's prior comment was that some of the medications that people use, such as NSAIDs, may be associated with angioedema. So other medication may contribute. But we took all of -- we looked at the indication for use and all of this information, and we took it into account when we performed our causality assessment. And so this is where we kind of fell out.

DR. O. JONES: And this is not a question but a comment. I really appreciate so much about FDA's effort on this. These children, particularly pediatric population, using biologics is still a learning curve. And picking up a signal from one case is really remarkable. Thank you very, very much. I think this is very helpful to us.

And I know this is not in the context of the meeting, but any data that can help us to identify the

existing immune dysregulation on these children who may be more at risk for these kind of adverse effects and FDA's suggestions -- coordinations will be greatly appreciated on that. I think many of my colleagues will be glad to be very sensitive about providing information. Thank you.

DR. WADE: Kelly Wade. Thank you. I think our final concluding question will come Dr. Czaja. You might need to unmute. Can we make sure that Dr. Czaja's phone is unmuted?

DR. CZAJA: Can you hear me now?

DR. WADE: Yes.

DR. CZAJA: Oh, okay. Thanks. Yeah. This is Angela Czaja. And my question's stems a bit from Randi's question earlier. I'm not exactly clear what a "no" vote would mean on this question. So I just wanted to make sure I understood, if I were to vote "no," what exactly that means.

DR. McCUNE: So this is Suzie McCune from OPT. I think a "no" vote would mean that you would want additional post-marketing safety monitoring. And we

would like to hear what additional post-marketing safety monitoring you would be interested in.

DR. CZAJA: Thank you very much. It's helpful.

DR. WADE: Kelly Wade here. Well, I'd like to thank the Committee for that robust discussion and Lisa Harinstein for offering all those responses to this review of abatacept and just acknowledge, as was previously pointed out, that this was a very important pediatric post-marketing safety review because in the trigger response and review, it sound an -- what appeared to be an important safety signal that was predominantly in adults. So it's a really nice affirmation of the process laid out before us and that at least one-third of the cases were delayed onset. So I know that this review was very much appreciated by the Committee -- and also the changes in the label.

So the question before us is -- we're going to move into voting, and the question before us is on the slide. The FDA recommends to continue ongoing post-marketing safety monitoring, and does the Pediatric

Advisory Committee concur with that? If there's no further discussion on this question, we will now begin the voting process. You should have received an email from the Pediatric Advisory Committee -- pediatricadvisorycommittee_vote with voting instructions.

Again, the instructions are to Reply All and when responding, type your vote "yes," "no," or "abstain" in the body of the email and nothing else. In case you encounter difficulties, please email your assigned point of contact or the ocoptpacteam email address. We will now begin voting on Orencia, and you will have 60 seconds to respond to the voting question.

(Pause)

This concludes our voting time. If you've not already submitted your vote, please do so immediately. We will now take a short break while the FDA compiles the vote.

DR. McCUNE: Dr. Wade, this is Suzie McCune. Yeah. We lost -- you were faint for a few minutes.

DR. WADE: Oh. I'm not sure what I'm doing

but thank you for giving me the heads up. That concludes our 60 second time window, and we will now take a ten-minute break or approximately thereof while the FDA compiles the votes. The vote will then be displayed, and Ms. Marieann Brill, our DFO, will read the vote from the screen into the record.

[BREAK]

DR. WADE: Kelly Wade. I believe the votes are coming. The voting slide is being put together and is about to be displayed. For the sake of time, I'm going to remind people that, once the vote is displayed on the screen, our Designated Federal Officer, Marieann Brill, will read the vote from the screen into the record. And then 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'll turn it over to Marieann Brill.

MS. BRILL: Hello. For the record, the voting results for Orencia are as follows: 21 "yes" and one "abstain." Again, 21 "yes," one "abstain." Thank you.

DR. WADE: Kelly Wade. Let's start at the top with Dr. Anne.

DR. ANNE: Premchand Anne. I voted yes.

DR. CALLAHAN: David Callahan. I voted yes.

DR. CUNNINGHAM: Melody Cunningham. I voted yes.

DR. CZAJA: Angela Czaja. I voted yes.

DR. DRACKER: Bob Dracker. I voted yes.

DR. FISCHER: Gwen Fischer. I voted yes.

DR. FLICK: Randall Flick. I voted yes.

DR. WADE: Kelly Wade. Just to let you know, Sarah Hoehn is next. You may be muted.

DR. HOEHN: I was waiting for Dr. Havens. Sarah Hoehn. Yes.

DR. HOLUBKOV: This is Rich Holubkov. I voted yes.

DR. B. JONES: Bridgette Jones. I vote yes. I just wanted to say that I think this is a model case for the benefit of the pediatric post-marketing surveillance, where -- in demonstrating that this activity or this surveillance not only benefits

children but also may benefit adults too because I think this is an important finding of angioedema in relationship to use of this medication. Although there are some caveats here where the patients may have been on ibuprofen, angioedema in general is rare even in patients that use ibuprofen. So ibuprofen is something that's in all of our medicine cabinets, but angioedema is something that in general is pretty rare. So I think this is an important finding. And again, I applaud the current pediatric process.

DR. O. JONES: Olcay Jones. I voted yes. And again, thank you for the excellent pick up. Thanks.

DR. WADE: Jeffrey Lukish is up next.

(Pause)

This is Kelly Wade. I'm wondering if Jeffrey Lukish is muted? His vote is to be reported next.

DR. LUKISH: Jeffrey Lukish votes yes.

DR. WADE: Thank you.

DR. McGOUGH: Jim McGough -- Jim McGough is yes.

DR. WADE: Dr. McMillan is up next. Dr.

McMillan, might you be muted? Let's keep going down the list and we'll return. Dr. Ortiz.

DR. ORTIZ-AGUAYO: I voted yes.

MS. OSTER: This is Randi Oster. I abstained with the reason that I support the labeling coming in June 2020. And I am abstaining because I want to call attention to the fact that I want the label addition to be very clear and that we should relook at Diana Zuckerman's points that she made earlier as the label is written for the market.

DR. PLUMB: This is Jen Plumb. I voted yes.

DR. SAYEJ: This is Wael Sayej. I voted yes.

DR. STRAWN: This is Jeffrey Strawn. I also voted yes.

DR. TURER: This is Christy Turer. I voted yes.

DR. WILFOND: And this is Ben Wilfond. I voted yes.

DR. WADE: Kelly Wade. We will now circle back to a few people. We had some audio problems. First up is Peter Havens.

DR. HAVENS: This is Peter Havens. I voted yes.

DR. WADE: Thank you. And Dr. McMillan?

(Pause)

Well, I think we're still having audio problems with Dr. McMillan.

DR. McMILLAN: I'm sorry. Can you hear me now?

DR. WADE: Yes.

DR. McMILLAN: Okay. This is Gigi McMillan. I voted yes.

GAMUNEX-C (IMMUNE GLOBULIN INTRAVENOUS [HUMAN]), 10%, CAPRYLATE/CHROMATOGRAPHY PURIFIED

DR. WADE: Thank you, everyone. Thank you for your patience in this voting process virtually. Pushing forward, we are now going to move into the FDA presentation on Gamunex-C, starting with a presentation -- that presentation, which I believe will be presented live.

DR. ZINDERMAN: Hi. This is Craig Zinderman.

Can I just get somebody to confirm they can hear me?

DR. WADE: Yes. I can hear you, Dr. Zinderman.

DR. ZINDERMAN: Great. Thank you. So this is Craig Zinderman, Associate Director for Product Safety with OBE Division of Epidemiology in the Center for Biologics Evaluation and Research. I'm going to be discussing our pediatric review of Gamunex-C and, in particular, hypersensitivity reactions that we've been monitoring in patients receiving certain product lots. We'll start with reviewing the product and the adverse events observed during the PAC review period, and then we'll go over the hypersensitivity reaction issues.

Woops. Sorry about that. Gamunex is a human immunoglobulin administered intravenous or subcutaneously. It is manufactured by Grifols. It was initially approved in August of 2003 for the indications of primary humoral immunodeficiency, idiopathic thrombocytopenic purpura, and chronic inflammatory demyelinating polyneuropathy. In December of 2015, the indication was expanded to include

administration by the subcutaneous route for pediatric patients with PI. This change in indication was the trigger for this Pediatric Advisory Committee safety and utilization review.

This table displays the counts of adverse events reported to the FDA over the original PAC review period from December 4th, 2015 through August of 2019. During this period, there were 95 reports in pediatric patients, including 38 serious reports and three foreign serious reports and two deaths. This slide displays an extended review period through the most recent nine months up to June 1st of 2020. During this extended period from September to June, there were an additional 23 pediatric reports of which 12 were serious, 11 from the U.S. and one was foreign. There were no pediatric deaths during this period.

FDA medical officers reviewed the narratives of all the serious adverse events and deaths in pediatric reports. Details of that review and the serious and non-serious adverse events are in our written safety and utilization review. The most common

adverse events among serious pediatric reports included urticaria, infusion-related reactions, dyspnea, rash, hemolytic anemia, headache, hypotension, and pyrexia.

In the beginning of the PAC review period and through July of 2018, there had typically been less than two to three hypersensitivity adverse event reports per lot of Gamunex. Up until that time there had been no lot withdrawals or recalls for hypersensitivity reactions or any other reason. Beginning in August of 2018, an increase in hypersensitivity-type adverse event reports was observed with certain product lots.

The most common adverse events reported in these events were urticaria, pruritus, rash, and lip swelling. Onset of symptoms was usually during an infusion of Gamunex or shortly after. In many of the reports for which we had information on the outcome, many of these reports resolved on their own, although some patients did require emergency room visits and received treatment with antihistamines or steroids.

While hypersensitivity is a known risk for

intravenous immunoglobulins, including Gamunex -- it is a labeled event -- the number of such events was elevated in eight Gamunex lots which the manufacturer elected to voluntarily withdraw to prevent any further events. This table displays the lot number for each of those lots, the total number of hypersensitivity event reports in each lot, including the number that were serious, and the number of pediatric reports for each lot, along with the date the lot was withdrawn. There were a total of 271 reports of hypersensitivity events from the withdrawn lots, including 107 of which were serious. There were no deaths associated with withdrawn lots. Of the 271 total reports from these lots, 25 events were in pediatric patients of which 15 were serious. These included cases of anaphylaxis, respiratory distress, urticaria, and rash.

Several actions have been taken in response to this safety issue. As I noted, the manufacturer has withdrawn eight product lots. FDA communicated this issue by publicly posting hypersensitivity events as a potential signal of serious risk in September 2019. In

addition, FDA continues to closely monitor for and review all reports of hypersensitivity events, as well as ongoing monitoring for the number of serious and non-serious incoming adverse events by product lot.

We have also instituted enhanced pharmacovigilance by requiring that the manufacturer report all hypersensitivity-type adverse events to FDA within 15 days as expedited reports despite this being a labeled event. FDA is engaged in ongoing discussions with the manufacturer to further evaluate the root cause and the investigation of implicated lots. As I noted, there were no deaths associated with withdrawn lots of Gamunex-C. A post-marketing pediatric safety review includes passive surveillance, adverse event reports, the sponsor's periodic safety reports, and the published literature for Gamunex-C. Most adverse event reports were labeled events and commonly associated with the immune globulin product class. Hypersensitivity is a known risk and a labeled event.

And as has been described, since August of 2018 there have been eight voluntary withdrawals for

Gamunex-C lots associated with increased hypersensitivity reactions. There have been no additional voluntary lot withdrawals since the beginning of this year. FDA recommends continued routine safety monitoring along with close monitoring of all reports of hypersensitivity including the lot-specific analyses. We'll also continue discussions with the manufacturer to further investigate the root cause. Does the Committee agree with FDA's conclusions and recommendations?

COMMITTEE DISCUSSION AND VOTE

DR. WADE: Thank you, Dr. Zinderman. This is Kelly Wade. We will now move forward with Slide 21 of the Gamunex-C voting slide and ask the members of the Committee for clarifying questions for the presenter today.

For Gamunex-C, the FDA recommendations for Gamunex-C include routine safety monitoring, close monitoring of all reports of hypersensitivity, including lot-specific analyses, and ongoing continue -

- sorry -- continued discussions with the manufacturer to further investigate root cause. The question: does the Committee agree with the FDA's conclusion and recommendation? Again, we will raise the hand signal so that I may call on you. We will start with Dr. Bridgette Jones.

DR. B. JONES: Yes. This is Bridgette Jones. I was wondering if the FDA could provide any more specifics around what it means to have continued discussion with the manufacturer? Is the manufacturer required to do some type of standardized reporting, or are there certain information that the FDA is requesting from the manufacturer? I just like to know a little bit more about what the discussion part means because these hypersensitivity reactions, although they're labeled -- but it's concerning when you see these repeated batches within a specific product.

And I say that because, not just a hypersensitivity reaction itself puts the patients at risk, but also these therapies are used for patients with primary immune deficiency where a subcutaneous

dosing of IGG we know provides a better steady-state level for their IGG level, which leads to improved outcome for these patients. So often what happens if the patient has a hypersensitivity reaction to a subcutaneous product, they're immediately pulled from that product by their provider. Their physician maybe isn't comfortable trying it again and the family as well.

And so then they're often transitioned to IV immunoglobulin therapy, which we know doesn't work as well for our primary immune deficiency patients in preventing, like, chronic lung disease, as well the impact of quality of life for these families when they have to switch from the subcutaneous product to a IV product. Where the subcutaneous product they can give at home, and IV infusions they have to come into our hospitals for that. So I just wanted to know if there were any more specifics around what they required from the sponsors in regards to identifying the root cause of these reactions.

DR. ZINDERMAN: This is Craig Zinderman.

Thanks for the question. I'll just review that we continue to monitor all reports of hypersensitivity, including by lot, and conduct lot analysis on an ongoing basis. Approaches for the root cause investigation has been under discussion with the FDA. And Grifols has identified an association between implicated lots that they're further evaluating. I don't have additional information about what those are -- what those steps that I can share right now. But I'll -- happy to open it up to others from our Office of Tissues and Advanced Therapies who might have other comment.

DR. WADE: Kelly Wade. Thank you. The next question, a clarifying question is from Dr. Dracker.

(Pause)

Dr. Dracker, you're up next for the clarifying question.

DR. DRACKER: Sorry. I was on mute. This is Bob Dracker. I just had a couple of questions and comments. The first is that the subcutaneous form is a fairly high incidence of local reactions which

sometimes in children have more complaints rather than just about the local discomfort but just become intolerable. And with regards to the parenteral form, are we collecting data with regards to infusion rates when patients have reactions? And also, even though I know Gamunex has a very low IGA level in it, did you collect any information regarding the IGA deficiencies in the patients who had reactions? Thank you.

DR. ZINDERMAN: This is Craig Zinderman again. So those are good questions. Typically in adverse event reports that we receive we don't have information on the rate of the infusion or the IGE -- IGA level. Information is often incomplete, and so those are details that we don't necessarily have.

DR. WADE: Thank you. This is Kelly Wade. I received information that Dr. Dot Scott from CBER also has a clarifying information for the prior question.

DR. SCOTT: Yes. Can you hear me?

DR. WADE: Yes.

DR. SCOTT: Okay great. So I think that Dr. Jones asked about more specifics concerning discussions

about the root cause investigation. And while I can't say much, I will say this is not the first time we've had a product. Other products have had this kind of problem, but there are more lots involved and a greater persistence. This just isn't a one-off situation. So in the past many, many firms have tried to come up with a root cause, anything as simple as measuring the amount of IGE in products and as complicated as doing in vivo studies even in primates or other animals.

So as yet not only -- we all remain mystified. Nevertheless, I would say that Grifols has undertaken a very serious investigation and a very extensive investigation. And the general categories of that investigation are looking at the manufacturing process, studying the products that were implicated compared with other products -- their own product, rather, compared with product lots that did not have this problem. And also looking at the donors, particularly to see if there are donors in common to these what we call here allergic lots as a shorthand. Thank you.

DR. WADE: Thank you. Thank you, Dr. Scott.

DR. SCOTT: So we actually speak with them every month or two about their investigation, and we try to do a little bit of our own work in thinking about what else can be done using not only their experience but the experiences that we've had with these in the past.

DR. WADE: Thank you. The next question comes from Dr. Peter Havens.

DR. HAVENS: On the slide that showed the number of reactions by lot number are there comparator products, either different lots that had a smaller number or are there products that would give us some perspective on the size of this problem? What's the usual number of responses?

DR. ZINDERMAN: Yeah. So we looked back at Gamunex lots prior to the start of this problem. While this is a labeled event, you do get hypersensitivity events with IVIg really, all IVIg products. Historically the number of reports that we typically see per lot for Gamunex runs around two to three reports and usually one or two serious reports.

So this is definitely an increase over the background that we had seen with Gamunex. And I'd say that's probably pretty similar to other immune globulin products, as well, you see generally as sort of a basal rate of hypersensitivity or allergic-type reactions. And it's fairly low numbers, three or four per lot, something like that. So these clusters represented an elevation.

DR. HAVENS: And so when does the size of the problem get big enough that you say they shouldn't be distributing it anymore?

DR. ZINDERMAN: So that's -- obviously, something that we have to consider. At this point, we're not seeing an elevation in lots since the beginning of this year. So when we see this elevation, the manufacturer chose to withdraw all of those lots. As the root cause investigation continues, we're not seeing additional lots with elevated rates that are significant enough to lead to withdrawal. And I think we're not at a place of deciding that it shouldn't be available. Dr. Scott or others might have comments as

well.

DR. HAVENS: Great. Thank you. That's very helpful. Thanks, thanks.

DR. WADE: Kelly Wade. Just to clarify, you told us about the eight lots that were recalled. But what's the denominator of like, how many lots were released in 2019 or in a similar period of time that were not recalled?

DR. ZINDERMAN: I don't have that number. My understanding is there's many more lots that were available during the same time period or released during 2019 that were not recalled. But I don't have exact numbers.

DR. WADE: That's okay. That gave us at least a (Inaudible).

DR. SCOTT: This is Dr. Scott. It would be on the order of hundreds of lots at least.

DR. WADE: Thank you, Dr. Scott. I believe the last clarifying question will be from Randi Oster.

MS. OSTER: Yes. Hi. Randi Oster, the Consumer Representative. I'm going to ask a question,

and then I'll explain why I'm asking that question. The question is you mentioned 271 reports of hypersensitivity, and I want to know if you have the breakdown by race?

I want to now explain why I'm asking that question. In the initial study, there were 12 subjects that were looked at, and they were all Caucasian. And according to Table 14.3, 11 went through the study where they had 69 adverse reactions, and that included site pain. The issue is that there is literature that states the ethnic differences in pain and pain management, and the conclusion by Dr. Campbell and Dr. Edwards is that ethnic groups may differ in outcomes for treatments. And we need to consider ethnicity as one factor.

Assuming that we don't know what the race is, I think looking at Caucasians only in this situation is lacking. And therefore a "no" vote would require, in my mind, the FDA to broaden the scope of who they do their testing on. So if you just can comment on the race breakdown of your 271 subjects?

DR. ZINDERMAN: Thanks. I don't have information on the race breakdown. It is collected on that in adverse event reports, and it is something that we would look at. And the company sees that as well when they do follow up investigation of these cases. I don't have that information in front of me. We did not identify a demographic trend with respect to these 271 adverse event reports, but I would have to find that information and get it back to you.

MS. OSTER: Okay. And I want to --

DR. ZINDERMAN: Most of the -- most of the -- I'm sorry. As you suspected, most of the time the race information is not available.

MS. OSTER: Right. And just as a global comment, the 2018 U.S. Census Bureau estimates that more than 50 percent of the population under 15 is non-white. So we do need to -- or so in my mind a "no" vote will be a methodology for us to expand when we're starting to look at different populations.

DR. McCUNE: Dr. Wade, this is Suzie McCune.

DR. WADE: Go ahead.

DR. McCUNE: I just wanted to respond. Ms. Oster, I think that you make some really excellent points. I just want to remind everyone that the FAERS and the adverse event reporting systems that are utilized by the FDA are a passive reporting system, and so we don't control who responds. Although clearly, we want to make sure and we want to communicate to the public that we want everyone to submit all adverse events reports. We know that adverse event reporting is under reported. But it is a passive system so we wouldn't -- but we are really at the mercy of the folks who do submit the reports.

DR. WADE: Kelly Wade. Thank you for clarifying that. Certainly, we are limited by the information at hand. Are there any further questions? I think we've called -- oh. Dr. Jones, and then we really do need to move on for voting.

DR. O. JONES: Thank you, Dr. Wade. This is Olcay Jones. As a curiosity, when a signal like that occurs, is there a mechanism within the FDA to have different products -- brand products tested in vitro,

in animal studies? Do you have any mechanism to not only depend on the company's input, but do you have any internal quality control measures? Thank you.

DR. SCOTT: This is Dr. Scott.

DR. ZINDERMAN: This is Craig Zinderman. I defer that question to -- thanks.

DR. SCOTT: I'm here. This is Dr. Scott.

DR. ZINDERMAN: Go ahead, doctor.

DR. SCOTT: So yes. Well, I can say quickly that I wish we did. But we do have the capability to do certain tests on products, but those tend to be more routine sorts of tests. And what this really calls for is non-routine sorts of tests. We have asked the firms to do some of those -- I mean firms in general and this one as well to -- we've suggested certain kinds of tests. And they've been very willing to do those.

We can look at simple things, but we don't have a lab set up specifically to address markers of allergy. But there are some very common ones that you can get commercial test kits for, and we have not done that. We actually think that -- well, we have those

sorts of results from a lot of firms. And we have done such tests in past cases, not for this product, and really found nothing informative.

And I think the problem is there is not currently any test for any of these situations that has been shown to differentiate allergic from non-allergic lots. And it is not for lack of trying -- I mean, in general. I'm not talking about Grifols specifically. These include in vivo studies, in vitro cell-based studies looking for triggering of, for example -- of histamine release and all sorts of -- ELISA, binding tests, cytokines, lots of things. And it remains a mystery.

I would say one of the hypotheses -- and I will stop taking up time -- is that maybe one or several donors even might have an antibody that can cause allergic events in other people. But we just don't know. And it's still being sought, and there's still work to be done. And it takes a while to do it.

DR. O. JONES: Thank you.

DR. WADE: Kelly Wade. Thank you to the

members of the PAC and the responders, both Dr. Zinderman and Dr. Scott, for providing that valuable discussion on Gamunex-C and the hypersensitivity reactions and lot withdrawals over the past couple of years. If there are no questions or comments concerning the wording of the question, we will proceed with voting.

You should have received an email from the pediatricadvisorycommittee_vote with voting instructions. The instruction is to Reply All to the message. When responding, type your vote "yes," "no," or "abstain" in the body of the email and nothing else. In case you encounter technical difficulties, please email your assigned point of contact. Please start voting on the Gamunex-C. You will have 60 seconds to respond to the voting question.

(Pause)

Okay. One minute has passed. If you have not submitted your vote via the email response Reply All, please do so immediately. We will now take an approximately ten-minute break while the FDA compiles

the votes. The votes will then be displayed on the screen, and our DFO will read the vote from the screen into the record.

[BREAK]

DR. WADE: Kelly Wade. Welcome back. Within a minute we'll be showing the polling slide. There it is. Again, I want to thank the Pediatric Committee for being patient with this virtual voting process. And I will ask Ms. Marieann Brill to read the vote for the record.

MS. BRILL: Hello, good afternoon. For the record, the results of the Gamunex-C -- the voting results of Gamunex-C are as follows: 21 "yes" and one "no," again, 21 "yes" and one "no." Thank you.

DR. WADE: Thank you, Marieann. Now that the vote is complete, we will go down the meeting roster and have everyone who voted state their name, their vote, and, if you want, you can state the reason why you voted as you did into the record, starting at the top with Dr. Anne.

DR. ANNE: Premchand Anne. I voted yes.

DR. CALLAHAN: David Callahan. I voted yes.

DR. WADE: Dr. Cunningham, you're up next. You may need to unmute.

DR. CUNNINGHAM: I don't know if you heard me. Melody Cunningham. I voted yes.

DR. WADE: Thank you. I heard you that time. Dr. Czaja.

DR. CZAJA: Angela Czaja. I voted yes.

DR. DRACKER: Bob Dracker, yes.

DR. FISCHER: Gwen Fischer, yes.

DR. FLICK: Randall Flick, yes.

DR. HAVENS: Peter Havens, yes.

DR. HOEHN: Sarah Hoehn, yes.

DR. HOLUBKOV: Rich Holubkov voted yes.

DR. B. JONES: Bridgette Jones, yes.

DR. O. JONES: Olcay Jones, yes.

DR. LUKISH: Jeffrey Lukish, yes.

DR. McGOUGH: Jim McGough, yes.

DR. McMILLAN: Gigi McMillan, yes.

DR. ORTIZ-AGUAYO: Roberto Ortiz, yes.

DR. WADE: Randi Oster, you're unmuted.

MS. OSTER: Oh, thank you. Randi Oster. I voted no. And the intention is this case is as the close monitoring of all the reports of hypersensitivity continues, I would like some effort to look at different ethnicities and to see if there are any differences and anything we can do the support of more global look at the population.

DR. PLUMB: This is Jennifer Plumb. I voted yes.

DR. SAYEJ: This is Wael Sayej. I voted yes.

DR. STRAWN: Jeffrey Strawn. I vote yes.

DR. TURER: Christy Turer. I voted yes.

DR. WADE: Ben Wilfond, you may be muted. You're up next.

(Pause)

Can we makes sure Dr. Wilfond is unmuted?

(Pause)

Dr. Wilfond, I wonder if you're locally muted on your own phone side of thing?

(Pause)

Again, maybe this will be our last call for

Dr. Wilfond to state his vote into the record. If you're trying to do so, we're having trouble hearing you. If you're having trouble with your audio, Dr. Wilfond, you might consider using the chat box.

DR. WILFOND: Oh. There we go. I got it. Sorry about that.

DR. WADE: Great. Thank you.

DR. WILFOND: Yes, yes. I voted yes. I'm sorry about that.

DR. WADE: Just state your name.

DR. WILFOND: Oh. Ben Wilfond.

DR. WADE: Thank you.

DR. WILFOND: I vote yes.

DR. WADE: Kelly Wade here. I appreciate everyone's patience. For the sake of time we are running over an hour late, so with the breaks built into our voting sessions, we're going to continue to move forward. We may need to be concise in our questions. And I would ask members of the committee, if they could, to please adjust their calendars because we will be finishing a little bit late today, at least

5:00 or maybe 5:15. But we want to give ample time for the Flourish discussion.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

ANNUAL UPDATE OF POST-MARKET HUMANITARIAN DEVICE EXEMPTION (HDE) REVIEW

FLOURISH PEDIATRIC ESOPHAGEAL ATRESIA DEVICE (HDE)

DR. WADE: I'll now ask for the next FDA presentation from the Center for Device and Radiological Health otherwise known as CDRH to update us on Flourish. This will be Dr. Priya Venkataraman.

DR. VENKATARAMAN-RAO: Hi. Can you guys hear me?

DR. WADE: Yes. Your audio is great.

DR. VENKATARAMAN-RAO: Okay. Hello and good afternoon. My name is Priya Venkataraman-Rao, and I am a medical officer that used to be on the Gastroenterology and Endoscopy Devices team that reviewed this device. I will be presenting a summary of the second annual post-market review data for the Flourish Pediatric Esophageal Atresia Device, which

includes a review of post-approval use, medical device reports, and published literature.

Before I get started, I wanted to provide a quick overview of the HDE program. This program is for devices intended to benefit patients in the diagnosis or treatment of diseases affecting less than 8,000 individuals in the U.S. per year. To approve an HDE application, the following criteria must be met.

The device should not expose patients to an unreasonable or significant risk of injury and that the probable benefit to health from device use outweighs the risk of injury from its use, taking into account the benefits and risks of alternative forms of treatment. I have italicized the term "probable benefit" to illustrate the difference between these types of submissions where the proposed patient population is small and regular marketing submissions that require safety and effectiveness for approval. The devices that are approved and labeled for pediatric patients are required to be reviewed annually by you all, the PAC, to ensure that the HDE remains

appropriate for the pediatric population for which it was approved.

Esophageal atresia or EA is a developmental arrest of the esophagus resulting in the absence of a lumen. The overall incidence of EA/tracheoesophageal fistula, or TEF, ranges from one in 2,500 to 4,500 live births. There are five types of EA, and classification is determined by the location of the atresia and the presence of an associated fistula to the trachea.

Flourish is to be used in patients with Type A and Type C EA. Type A is an isolated atresia without a TEF. And Type C is an atresia with a distal TEF that has been closed as a result of a prior procedure.

In this slide on the left you see that in a person with a normal esophagus, if you insert a nasogastric tube, it will end in the stomach. I copied this figure over to show that, in the types of esophageal atresia we are talking about, the upper esophagus ends in a pouch that you can see in red. On the bottom is a radiographic image that shows an oral or nasogastric tube that is coiling on itself in the

upper esophagus because it is a pouch and noncontinuous with the lower esophagus.

Because of this noncontinuous esophagus, infants usually present with excessive oral secretions, feeding intolerance, and/or respiratory difficulties, depending on what type of EA/TEF they have. This necessitates suctioning and feeding through a gastrectomy tube for nutrition. Morbidity and mortality is also dependent on the commonly associated conditions of VACTERL, which stands for vertebral, anal, cardiac, tracheal, esophageal, renal, and limb. And the CHARGE association which stands for coloboma, heart, atresia, choanal, retarded growth, genital hypoplasia, and ear deformities.

Current standard of care includes surgical repair via thoracotomy or thoracoscopy to create an anastomosis between the two esophageal segments. Risks include anesthesia, post-op pain, leak, stenosis, reflux, dysmotility, and fistula recurrence. Deformities of the thoracic wall can occur later in life and can include shoulder weakness, winged scapula,

or scoliosis. Understandably, these deformities can be very disfiguring and cause psychological effects. If repair is unsuccessful, colonic, gastric, or jejunal interposition are options.

The IFU is stated on this page. Instead of reading it word for word, I will highlight that the device is used to create an anastomosis in infants up to one year of age with esophageal atresia in which the esophageal segments are less than four centimeters apart. The device consists of an esophageal catheter and a gastric catheter, with distal ends of both catheters containing magnets. In a candidate infant, the distance between the atretic segments is assessed under fluoroscopy. After identification of the pouches, the esophageal and gastric catheters are inserted orally and through the gastrostomy stoma and advanced until the magnets are located at the distal end of each pouch. Within approximately three to 13 days, the traction caused by the magnets allows the two pouches to approximate.

Daily chest X-rays are taken to assess the

distance between the magnets. Once approximated, the surrounding tissues grow together while the tissue between the magnets necrose, causing the anastomosis. Once an anastomosis has been confirmed, the magnets are removed. An OG or NG tube is then placed.

These chest X-rays show the different steps in the process. In A, the X-ray is performed to determine the length of the gap. In B, the image is verifying magnet placement. In C, you see the coupling of the magnet. And D is the first esophogram after anastomosis showing the flow of contrast through a patent lumen.

FDA relied upon two articles from the literature to grant the HDE submission. In the first article, nine patients from a single center in Argentina were treated with the device. All nine achieved anastomosis. However, eight out of nine also developed anastomotic strictures that required dilation with two of these with intractable stenosis also undergoing stent placement. There was one patient who underwent both several dilations and stent placement

who ultimately required surgical re-anastomosis.

In the second article of two cases, both achieved anastomosis, but both also developed strictures. For the remaining patients, FDA relied upon information submitted in five emergency use case reports. All achieved anastomosis, but three out five developed stricture as well. In totality, we had data from 16 patients, all of whom achieved anastomosis but 13 also developing anastomotic strictures that required intervention. This stricture rate was higher than what was reported for standard of care surgical repair that was estimated to be around 30 to 40 percent. However, anastomotic repair could occur earlier than surgical repair and avoid several surgical complications. Therefore, it was concluded that the probable benefit of earlier anastomotic repair and fewer surgical complications outweighed the risks of the higher rate of anastomotic strictures requiring balloon dilation and/or esophageal stenting in the appropriate patient, and the HDE was granted.

To help obtain longer-term data on

stricturing, a post-approval study was designed. This initially involved a minimum of 20 subjects in a prospective, single-arm, new enrollment observational study at 15 sites, at least one being in the U.S. with a two-year follow up. The primary endpoint would be rate of stricture as well as perianastomotic leaks and other adverse events that could be related to the device or procedure. The secondary endpoint would be successful anastomosis formation.

This table shows all the patients that have had the device placed since approval. As you can see, of the 20 patients, six were enrolled in the PAS study, and 14 were commercial-use cases. Due to a lower than expected rate of enrollment, in June of this year the sponsor notified FDA of their intent to modify the study design to increase enrollment and meet the requirement of providing complete data for 20 patients. FDA is currently interactively working with Cook to explore modifications of the PAS study in order to meet the PAS objectives.

This table shows a high-level overview of the

anastomosis data we have received thus far regarding PAS and non-PAS patients. The six PAS patients are outlined in blue and the 14 commercial cases in white. I will summarize the anastomosis information on the next slide. There is also an important labeling change that occurred in October of last year that I will be discussing in a few slides.

In the 16 cases pre-approval, there was anastomosis in all patients. However, in the post-approval cases, the rate dropped to 50 percent. This can be further broken down into success in the PAS patients, which is approximately 33 percent, and in the non-PAS patients, which was 57 percent. If we just look at all post-approval patients who received the device, whether they were in the PAS study or not, rate of anastomosis was 50 percent before a labeling change and 50 percent after the change.

The stricture rates are a little bit more difficult to ascertain since there is limited information. Of the two PAS patients reported to have formed an anastomosis, they both developed a stricture.

And there is no information available in the non-PAS patients. Therefore, the true stricture rate is unknown.

Taking a step back for a minute, following the fourth patient enrolled in the PAS, Cook submitted their regularly scheduled annual report. At that time because three out of four patients had not achieved anastomosis, which was different from the 100 percent anastomosis rate we saw pre-approval, the sponsor investigated potential causes for these anastomotic failures. For example, they evaluated device specifications, and non-clinical testing confirmed that magnet strength remained consistent with the devices that were used pre-approval. Clinically, the sponsor collaborated with a physician consultant who helped provide recommendations to improve anastomotic success that were put in the labeling.

This was the specific labeling change. I won't read it word for word but will highlight that the recommendations were to use flexible measuring tools versus rigid ones that may have led to inaccurate gap

measurement, imaging in two views, using a ruler, and verifying that gap measurement was truly less than four centimeters immediately prior to placing the device. FDA approved these labeling changes in October of 2019 based on the presumption that they would address the anastomotic failures that were observed in the initial PAS results. If you now recall the percentages of anastomosis success pre- and post-labeling change, it did not appear that it made quite the impact that we had hoped. Other potential reasons for the lower rate of success will be discussed later.

Now switching gears to the systematic literature review. This was performed using the method you see listed here. Two articles met the criteria. However, it is unclear if the patients in the articles were the same as previously reported in the article submitted for approval. Regardless, the data was consistent with the pre-market approval data with 100 percent anastomosis and high stricture rate. The long-term outcomes were encouraging in that most patients were tolerating full feeds.

An analysis was also performed to identify MDRs associated with device use. Ten MDRs were identified in the reporting period between four and 16 days after the procedure. In eight out of ten patients, anastomosis was not achieved. In the two patients that did achieve anastomosis, both developed a stricture. Leak and a fistula were also seen. As with the articles above, there is a possibility that these events may also be the same ones as were reported in the PAS and non-PAS patients. As per the sponsor, six out of the ten MDRs were on the same patients that were in the PAS.

In conclusion, the initial data demonstrated both a high anastomosis rate as well as high stricture rate. When balancing the benefit versus the risk, we concluded that earlier anastomotic repair and fewer surgical complications outweighed the risk of stricture development. The post-approval data give us a different picture with anastomotic rate dropping by almost half and limited stricture information.

We are still attempting to determine the

causes for these differences. The measurement technique and timing addressed by the labeling revision did improve outcome but not as much as would be expected if that was the sole issue. Other reasons may include selection bias, scarring of the esophageal ends from previous intervention, age and/or gender of the patient, site where the procedure was performed, atresia type, and/or physician experience.

From the very limited data that we have, scarring from previous intervention seems to be likely if the data is no better or worse when looked at by age, gender, site, or esophageal atresia type. We are still trying to obtain further information but, in the meantime, feel that it is still reasonable to conclude that the probable benefit outweighs risk when considering alternative forms of treatment. We therefore recommend continued surveillance of data and will report to the PAC next year annual distribution number, PAS follow up results, literature review, and MDR review.

Our question to the PAC is the FDA will report

on the following to the PAC in 2021: annual distribution number, PAS follow up results with the caveat of the revised PAS study that we are working in collaboration with the sponsor on, literature review, and MDR review. Does the Committee agree with the FDA's plan for continued surveillance of the Flourish device? Thank you.

COMMITTEE DISCUSSION

DR. WADE: Kelly Wade. Thank you very much, Dr. Venkataraman-Rao. That was an excellent presentation. Clearly, this is a very unusual and difficult condition to treat. There are a few hands going up, so we will now take clarifying questions for Dr. Venkataraman-Rao, the presenter. Remember to state your name for the record before you speak.

And if you can, please direct questions to a specific presenter. We do need to be mindful of our time this afternoon. And again, once your question has been answered, please make sure you take your hand down. I'm going to start today with our clarifying

questions first from Dr. Fischer.

DR. FISCHER: Hi. This is Gwen Fischer. Thank you for the presentation. Given that this is a HDE product, wondering if the surveillance can also include not just the stricture rate but also the re-intervention rate for those strictures and also feeding intolerance? I think that will provide a more accurate picture of risk versus benefit for a product like this.

DR. VENKATARAMAN-RAO: Priya Venkataraman-Rao. I agree with you. I think right now we are trying to work out what this revised post-approval study is going to look like. And these are all outcomes that FDA would definitely want to see -- to gather more information on. Thank you.

DR. WADE: Kelly Wade. Thank you. I'd now like to call on Dr. Jeffrey Lukish for clarifying question. He -- thank you for that unmute.

DR. LUKISH: Hi. Good afternoon, everybody. I'll try to be brief. Outstanding presentation with a very challenging and rare disorder. I wanted to comment to some of the things Dr. Zuckerman said in the

open forum, and I wasn't sure exactly if that the time to do it or now.

But the reality is, if you look at the difference between the entire group that you are comparing, the device is really, if you think about it -- is designed for the Type A atresia. And we're creating a Type A atresia by doing a surgical intervention in the Type C atresia, the one with the fistula. Those two groups are very much different and will likely respond very differently to the Flourish device because of what you've mentioned in your presentation, the scarring of the previous intervention to create the Type C into a Type A pure atresia.

And that's incorporating that patient population, the Type C atresia is probably important. Because when you look at the rarity of the pure atresia, which is the atresia with no connection to the trachea which is what the Flourish device would ideally treat, that anomaly is somewhere between a one in 60,000 and 1 in 80,000 live birth anomaly because it only represents 7 percent of an anomaly that occurs in

one in 5,000 births roughly. 85 percent of those are the Type C. So my question really is, well, one, it's a rare disorder without a very good intervention. And so utilizing this device as a novel way to approach a challenging problem where stricture in the best hands occurs when it's done minimally invasively or openly or with this device, I think the importance in defining carefully in your next round as to who you are using the device on is important.

Now, my one question is exactly how -- and I think whoever interpreted the data in terms of the gap size is a critical piece because anything greater than four centimeters is going to be very challenging to put together regardless of the way you repair it. And so how did they -- how are you going to determine that gap distance going forward? I understand that you are using a rigid technique, which may make the gap distance shorter than it actually is. And what is the technique that you are going to use in the next round?

DR. VENKATARAMAN-RAO: Priya Venkataraman-Rao. Thank you. Those are all great points. Just to

address your first comment about the Type A versus C, I think one of the challenges we're faced with is that we have such limited patients. So in the PAS patients, all this gets reported, what type of EA did they have and all the other kind of details that go around that.

And in the majority of the patients, the 14 commercial cases, we really don't have too much of that information. So we're kind of going on what we have. When we parse out the, well, how many were Type A or Type C that did or did not achieve anastomosis, we could really find no pattern. So I think the more patients there are, the better we can attain that information.

Okay. You had asked about gap size. I believe that one of the issues from previously was that that gap size was not being measured immediately before the device was placed. And so that was one part of it is make sure it really is only four centimeters or less than that because otherwise the magnetic forces are not going to attract. I know that the sponsor has examples of flexible tools that you can use instead of the rigid

ones. How that has worked since we got this data together for the presentation, I don't know that. I don't have that information. Did that answer your question?

DR. LUKISH: So it's very important -- for the FDA to determine whether the device has efficacy, it's very important to define what group of children the device is going to be used in. And in the children that are pure atresia type A, those children are being measured at very close to birth absolutely for sure because they are made -- the diagnosis is made because they have no air in their GI tract at birth, and they're aspirating saliva. Whereas the Type C patient is a child that's approached operatively, usually either through a thoracotomy or a thoracoscopy.

And those children are converted to an A because for some odd technical reason they could not be anastomosed in the classic fashion at the time and then are converted to A. And therefore, they are managed for several weeks and then are measured. And again, the way you measure the gap is critical for the FDA to

define whether the device can show efficacy and can be used.

I think it's important to note that there were no deaths in either the PAS pre or post. That's key because there are children that are approached through open procedures that have a very morbid outcome. So that's key that none of these children have passed away as a result of the device. But I think, again, it's important to define the two groups carefully so we can then evaluate that at the next round. And it may only be five or six patients. I think if you approach just the Type A, you will find a difference compared to the Type C. They're really two different patient populations.

DR. VENKATARAMAN-RAO: Thank you. Thank you for that information. We will definitely take that into consideration when revising the post-approval study.

DR. WADE: Kelly Wade here. I'd like to go ahead and move forward with the sponsor presentation of the Flourish device. And I suspect that we can then

regroup with the current line-up of questions as it stands: Flick, Sayej, Oster. I'll keep your hands raised or keep your hands up if you still have questions. And after the sponsor presentation, you can direct your questions to either the sponsor or Dr. Venkataraman-Rao from the FDA. I'll turn it over now to the sponsor.

SPONSOR PRESENTATION: FLOURISH™ PEDIATRIC ESOPHAGEAL ATRESIA DEVICE

DR. HEISE: Well, very good. Can you hear me okay?

DR. WADE: Yes. You sound great.

DR. HEISE: Great. Good afternoon. This is Ted Heise. I'm Vice President of Regulatory and Clinical at MED Institute. MED is a Cook Group company that focuses on research and development and is a sister to Cook Medical. So I am an employee of the sponsor.

We thank you for the opportunity to present our experience with the Flourish Pediatric Esophageal

Atresia device. We are excited to be here today and are happy to provide information to support your deliberations on this product. We recognize the hour is growing late, so we'll be as efficient as possible.

An important context for discussion today, as Dr. Venkataraman-Rao pointed out, is that this is a device that may prevent the need for surgery. Admittedly, it is not a perfect device. And in our commercial experience to date we're not seeing safety issues. From your briefing material as well as the FDA presentation, you should appreciate that the Flourish device was developed for a very small patient population. As such there are added barriers to commercialization that almost prohibit the undertaking.

I'm very proud to work for a company that is willing to pursue options to serve the needs of these few patients despite the challenges. In making this product available, Cook has put considerable effort into doing so with the focus on safety, for example, by requesting and reviewing imaging to assess suitability each time a device is requested as well as providing

in-person support of each case. Let's now turn to the agenda for today.

It looks like we've got some problems with the format of the slide. Would it be possible to go to the PDF version? We don't have all of the information showing on the slides. While they're pulling that up, let me forge ahead, and I'll walk you through the agenda.

We'll start with a very brief company overview with our commitment to unmet patient needs. We are privileged to have a couple of prominent physicians in this area to also share -- ah, that looks perfect -- Dr. Zaritzky and Dr. Slater, both from the University of Chicago School of Medicine, who have experience with the patient population and the device, will describe the clinical need and the impact of open surgery. And I'll give just a high-level summary of the post-approval experience and challenges unique to this setting.

Cook Medical was founded in 1963. It is a family-owned, multinational medical device manufacturer

with world headquarters in Bloomington, Indiana. The division that developed and manufactures the Flourish device, our Endoscopy Division, is headquartered in Winston-Salem, North Carolina.

The Cook Medical Company employs over 12,000 employees worldwide, 8,000 of which are employed in North America. We manufacture over 10,000 different products and innovate minimally invasive diagnostic and therapeutic products for the treatment of a wide variety of diseases. The company does have a long-term demonstrated commitment to pediatric patients. You will note that much of this record is specific to HDEs, not necessarily limited to pediatrics, but in our implementation, they have been focused primarily on pediatric products. Cook was a part of developing the enabling legislation for the Humanitarian Device Exemption pathway and also contributed to the implementing regulation.

The company did pioneer the first HDE approval, the Harrison Fetal Bladder Stent, in the 1990s. We have provided comments on all amendments of

HDE regulations, submitted and accepted National Evaluation System Technology Project to evaluate collecting real world data in support of a pediatric device approval. We are actively pursuing additional small-market pediatric products, for example, within the Harmonization by Doing for Children program and recently culminating in approval of the Flourish Atresia Device, a minimally invasive treatment option for select infants that avoids the need for major surgery.

At this point I'd like to introduce Dr. Mario Zaritzky, the inventor of the technology and probably the foremost clinical expert in its use. Dr. Zaritzky?

DR. ZARITZKY: Hi, hello. Thank you for the presentation. I am Dr. Mario Zaritzky. I am a former Argentinian board-certified pediatric surgeon and pediatric radiologist working now as the pediatric radiologist at the University of Chicago. I am also a paid consultant to the sponsor and receive royalties for the subject product.

Back in Argentina in 1995, I was treating

patients with the traditional method of open chest surgery, but I had the feeling there had to be something else less aggressive to treat those patients. So after researching in the topic, I start looking for a company who will share my idea, my passion, my vision, and my dream of using magnets for the treatment of esophageal atresia. It was a very difficult task until I crossed path with Cook.

Together, we are able to come up with an excellent device to treat these patients, and that's the device we are here to talk about today. To speak about the background of pediatric esophageal atresia and the clinical need, I elect now to introduce my colleague Dr. Bethany Slater. Thank you very much.

DR. SLATER: Great. Thank you. This is Bethany Slater. Are you able to hear me?

DR. WADE: Yes. You sound great.

DR. SLATER: Great. Thanks so much. Well, I'm one of the pediatric surgeons at the University of Chicago, and I have no financial disclosures related to this device. In patients with esophageal atresia, both

with and without tracheoesophageal fistula, they will historically undergo surgical repair sometime after birth, depending on their status and associated anomalies. And the picture at the top shows an open repair after a fistula has been repaired and the esophagus has been anastomosed.

However, there are a number of complications related to surgical repair, first of which is anastomotic leak which occurs in about 13 to 16 percent of patients. As seen in the esophagram on the right most patients will undergo an esophagram about a week after repair. And this shows evidence of a leak shown by the red arrow.

Oftentimes, patients can go non-operative management of a leak, but some do require a re-operation. Additionally, strictures are fairly common after surgical repair. And they can be seen in up to 11 to 80 percent of patients depending on how it's measured. As was mentioned earlier, many of these patients often require balloon dilatation to treat the strictures endoscopically. And repeated dilations are

not uncommon for these patients as well. Additionally, recurrent fistulas can occur in 3 to 14 percent of patients. And in addition to these shorter-term complications, a number of long-term complications are seen in these patients including gastroesophageal reflux, tracheomalacia, and other quality-of-life issues. Next slide, please.

Additionally, a systematic review has recently been done primarily looking at Type A and B esophageal repair for the last ten years which have fairly similar complication rates as I just cited. Next slide. They also note that the mortality rate is about 5 percent. And additional surgery for these patients were required in 8.6 percent of cases. Next slide.

In addition to these patients, the longer gap for patients in which the ends of the esophagus are difficult to bring together or unable to come together without tension make up a very technically challenging group of patients. And a variety of surgical techniques are used. But all of them have in common that they require multiple operations with repeated

anesthetic, as well as long operative times, and create a significant physiologic stress to these patients. Next slide.

So the Flourish device provides a non-surgical alternative for esophageal anastomosis. And the major benefit, as already stated, is that it avoids invasive surgical procedure. The main advantage is that it avoids dissection on both esophageal pouches. And this allows for the potential for decreased dysmotility of the esophagus, decreased risk of injury to the recurrent laryngeal nerve.

And in addition, without operative repair, there's also no need to dissect and ligate the Azygos vein, which potentially prevents a rare potential for hemorrhagic events. In addition, this may be particularly beneficial for patients with cardiac or other anomalies that are often seen with these patients.

DR. HEISE: Thanks very much, Dr. Slater. I'll continue with a high-level summary of post-approval experience and challenges. The post-approval

experience has by and large been favorable. From HDE approval in May of 2017 to the end of May 2020, the Flourish device has been used in 21 infants.

You may note a slight discrepancy in numbers between what FDA presented and what we are presenting. There was one case that did not get reported quickly enough to FDA to make it into their final slides. The messages really are no different. We really, I think, agree with the interpretation FDA has presented to you for the most part.

Importantly, the cases have been scattered across 16 hospitals. Four of these are in -- four of these 21 are in Canada where the device has been used under special access provisions. Of the 21 infants treated, a total of 19 physicians have used the device. That means two physicians have each treated two cases. Of these 21 cases, six have agreed to enroll in the post-approval study.

Here's a high-level tabulation of the principal outcomes to date. I'm not going to go through it in detail. I'll just note that the rows are

dedicated to the two annual reporting intervals, the number of cases in the first column and the number of successes in the second column. And then importantly, adverse device effects are listed in the final column and show that there has been one esophageal pouch leak. This is an anticipated type of event, and it was also associated with use of the device outside of recommendations in the labeling.

So to sum up the post-approval experience, the rate of a successful anastomosis has increased slightly from 43 to 57 percent. Although these numbers are very small and it's difficult to discern any real meaning from a statistical standpoint, we also are aware that of the several cases that have occurred since the end of the reporting period being presented today nearly all of them have been successful in creating anastomoses. So these results suggest that the changes in labeling have improved case selection and outcomes in terms of success in achieving anastomosis.

As expected, adverse device effects that were anticipated in the labeling have been observed.

Balloon dilatation for stricture, though not uncommon, is also often necessary for infants whose esophageal atresia has been treated surgically. One case of esophageal leak observed was associated with use of device outside of recommendation, and no unanticipated adverse device effects have been reported to date. Importantly, we think it's necessary to call attention to the fact that infants without successful anastomosis remain candidates for surgery. Device use does not limit the options for these patients. Accordingly, based on all of the available information, we believe that the benefit to risk ratio remains favorable.

Changing gears slightly, we want to talk about the post-approval study challenges. These are based not only on our experience with the current study but experience from several decades of conducting clinical studies for medical devices. Most importantly, the patient population is very small. Most hospitals see only a single baby. Therefore, prospectively selecting and contracting investigative sites is problematic as it is impossible to predict at which hospitals these

babies will present until after they are born.

Even when we know, hospitals are often unable or unwilling to urgently complete the traditional clinical trial contracting process in the short time between diagnosis and the need for treatment. Having a required follow up schedule is inconsistent with an observation of standard of practice. And we don't believe it is required for assessment of the primary endpoint, as well as being impractical.

And then finally, physicians and parents often decline to participate in the study, especially in the setting where the device is already commercially available. As a result of all of these challenging factors, post-approval study enrollment has suffered, and many cases have not been included. An overview of the post-approval study status in year 3 is that despite extensive effort by the company, enrollment has been sparce, less than a 30 percent capture rate. Of the seven hospitals with prospective contracts and IRB approval, less than half have actually enrolled a case.

Additional reasons the physicians and/or

hospitals have declined to participate in the study include the necessity of redundant IRB approvals, specifically one for use of the -- or access to the HDE device and one for participation in the post-approval study. There's also been mention of possible inadequate insurance coverage. As Priya mentioned earlier, the sponsor is collaborating with FDA to develop a revised post-approval study plan. The company believes that this plan would provide data on the stricture rate, unreported adverse events, as well as outcomes for patients that proceeded to surgery.

So to sum up, the Flourish device provides an important minimally invasive treatment option for appropriate infants, often avoiding the need for major surgery. The clinical experience to date has been largely favorable. The rate of successful anastomosis appears to be improving.

No unanticipated adverse device effects have been reported to date, and the option to proceed to surgery, if needed, is preserved. Enrollment in the traditional post-approval study has been low as

expected. However, collaborating with FDA we believe we can develop a revised PAS plan to collect the necessary data. And then finally, the benefit ratio remains favorable in our view. Thank you very much.

COMMITTEE DISCUSSION AND VOTE

DR. WADE: This is Kelly Wade. Oh, sorry. My screen just went dark. Thank you for that excellent presentation from the sponsor team. I'm going to now ask that the members of the Advisory Committee be available for clarifying questions for either of the presentations this afternoon.

Again, we will use the "raise the hand" signal as many of you have done. And remember when I call on you, please state your name for the record before you speak. And if you can, please direct your questions to the specific presenter, particularly in this session where we have two presentations available for discussion.

Again, let's be mindful of the time. Follow the chat box where I have the order of people I'm going

to call on. And as previously stated, I'm going to start with Dr. Flick.

DR. FLICK: Thanks, Kelly. Randall Flick. This is a question I think probably for the sponsor but could be answered by the Agency as well. If I'm reading this right -- and first of all, I congratulate the sponsor on the work that they're doing here. Cook has done great work in pediatrics, and we appreciate that. But I am a little concerned that essentially all the information that we have about this device flows through either the inventor or the sponsor. And I don't see clear evidence here that there's any independent eyes on the depth and breadth of information on each one of these children on whom this device is used.

And maybe for the FDA to help me better understand how we as a Committee and the FDA as an agency monitors the use of these devices in a way that all of the information on each of these children is available in the sense of a data safety monitoring board or some independent view of the data?

DR. HEISE: So I guess I can take an initial comment at that. This is Ted Heise speaking. And I would say that within the formal post-approval study there is an established monitoring process. The revised study plan that's being developed will have, depending on how things are finalized, an additional quality assurance piece that will serve to assure reliability of the data. And I guess with that, I would ask if anyone from FDA would like to take on that comment from their perspective?

MR. ANTONINO: Hi, this is Mark Antonino. I'm a biologist and the lead reviewer for the HDE approval. So we have a HDE annual report in place in which Cook is to report an evaluation of safety regardless of the PAS study. And in addition to that, we also have the MDR program in place which captures medical device reports of adverse events that may occur regardless of whether or not they're used in the PAS study or not. So we have an active surveillance program to account for continued use of the device outside of PAS. Does that answer your question?

DR. FLICK: Well, to some extent. You know those of us who care for these patients, either surgery, anesthesia, neonatology, whatever, understand that these are very complex patients, and this is a complex issue. And I think in order to evaluate the data that comes in, one has to have a fairly significant level of expertise which I'm not sure exists within the Agency. And I just want to make sure that, going forward, that the reports that come out of the use of this device, whether it's within a study or outside a study, are robust and that they're evaluated by individuals who have the level of expertise necessary.

DR. HEISE: Well, Dr. Flick, maybe I can add one comment. Ted Heise again. I can state that MED Institute and Cook Research that are doing the data collection -- data management have been doing this work for decades. I certainly appreciate that industry is often viewed with suspicion. But I can also add that the company has undergone a considerable number of bioresearch monitoring inspections by FDA without any

483 observations over many dozens -- of many dozens and dozens of studies.

DR. FLICK: I appreciate that. I don't want to take any more time. But I think it's in your interests, certainly in the patient's interest, and it's in the Agency's interest to have independent view of these data. Otherwise, you recognize more than I do that that suspicion will not be reduced unless there's clarity around who evaluates the use of the device. I'll stop there, Kelly. I apologize for taking so much time.

DR. HEISE: No. Your point is well taken. Thank you.

MR. ANTONINO: Mark Antonino. I just -- Mark Antonino, FDA. Just to be clear, you know, in terms of expertise the Agency did utilize a network of experts approach when approving the HDE to provide an overview of all the information we had to date before we approved it. So where we don't have specific surgical expertise, or expertise to speak to this issue, we can find it, and we did in this circumstance. But we

appreciate your comment and input from the PAC, and we'll continue to think about that moving forward.

DR. WADE: Kelly Wade. Thank you for those excellent points. I want to continue to get through as many questions as we can. I'd like to call on Randi Oster.

MS. OSTER: Yes. Thank you. This is Randi Oster. And I'm putting on my mom hat here. My understanding is that this product currently is FDA approved (Inaudible).

MR. ANTONINO: Mark Antonino, FDA. Yes. It is FDA approved.

MS. OSTER: And so the reason I asked that is, as a mom if my child had to go through surgery, I know the comfort level I would have if I asked the doctor is this FDA approved and they say yes. And my expectation -- and I think it's shared by many parents -- is that means it's been tested, it's safe, and it works. And so my question is, knowing that we have such limited date here, why isn't this still in clinical trials? Why aren't we waiting to get more data and then say

it's an FDA approved product?

DR. ANTONINO: Mark Antonino, FDA. We have a guidance document which I can refer you to for further information. But in terms of HDEs, because of the rare nature of the disease, it is anticipated that we'll have a general -- a certain level of uncertainty -- greater uncertainty surrounding the benefit-risk profile in regard to evidence as opposed to other submissions of post-market approvals. So with this small population, we often anticipate there's a low amount of evidence that demonstrate a favorable benefit-risk profile.

MS. OSTER: I'm just not sure that parents understand the distinction. Thank you for answering the question.

DR. WADE: This is Kelly Wade here. Can you hear me? I had to call back in.

DR. HEISE: Yes. We can hear you.

MS. OSTER: We can hear you, Kelly.

DR. WADE: Sorry about that, everyone. I think your question was answered, Randi?

MS. OSTER: Yes.

DR. WADE: Great. Moving on, I'd like to call on Sarah Hoehn.

DR. HOEHN: Thank you. Sarah Hoehn. Happy to learn more about my University of Chicago colleagues as well. I have two questions that are sort of a combination of (Inaudible).

(Adobe Connect meeting restarted)

DR. WADE: Thanks for everyone's patience. It looks like we're almost through this. Thanks again to the excellent audio/visual support we're receiving today as we do a virtual meeting for the first time. Go ahead, Sarah Hoehn, and let's see if we can hear you. I believe we can. If not, if you type your question, I'll read it.

Sarah Hoehn, I don't think your audio is connected yet, but you can type away. In the meantime, it looks like Peter Havens has his audio connected. So let's do Dr. Haven's question. And then I will make sure I circle back to Sarah Hoehn.

DR. HAVENS: Thank you. Previously there was

a point made about Type C and Type A fistula types and how that might control the benefit of the device. Is there an ability to look at that going forward? That's number one.

And number two, you mentioned looking at this as a quality improvement project. Does that allow you to avoid some of the IRB requirements that seem to be such an impediment to getting a complete data set? It seems like we're sort of in the perfect is the enemy of good world here in terms of getting adequate capture of the data.

DR. HEISE: Yeah. So Ted Heise here. The quality improvement was not quite what I intended. I know what you mean, and we're not pursuing that exception under the HIPAA regulations. But we have built in quality assurance processes within the proposed data collection process to help provide reliability of the data that's actually collected. We do intend to be collecting the type of atresia as one of the important inputs in the data collection.

DR. HAVENS: Thank you.

DR. WADE: Thank you. Dr. Hoehn is back available audio. She has two questions. Go ahead, Dr. Hoehn. It looks like Dr. Hoehn is muted. You're open now, Dr. Hoehn.

DR. HOEHN: Can you hear me now?

DR. WADE: Yes.

DR. HOEHN: Oh good. Thank you. This is Sarah Hoehn, also University of Chicago. So my two questions were, number one, if there's any competing or similar devices on the market and, two, any use of this device that's not being presented in this forum? I think it was Dr. Slater who mentioned that there were some people who were choosing not to do it because the follow up was too burdensome. So I wanted some clarity around how, if someone has this device, are there -- can they sort of opt out of follow up, or are they choosing a different device instead? I just sort of needed clarity around how people would get to the choice.

DR. HEISE: So Ted Heise. I'll take a first shot at it. The device is commercially available as an

approved product. So there is access available without participating in the clinical study. The reluctance to enroll is in part because of probably in larger part for not wanting to wait for the treatment while the consenting process is under way.

The follow up and not being willing to follow up is always a potential barrier to participation in clinical studies. I'm not aware that it is a barrier for this particular patient population. My sense is they're pretty amenable to follow up. Maybe Dr. Slater would care to comment on that. Oh, she may not have gotten connected again yet.

MR. ANTONINO: Mark Antonino, FDA. While she's connecting, I can just add that FDA is not aware of other approved or cleared device for the preferred indication.

DR. SLATER: Hi. This is Bethany Slater. Can you hear me?

DR. WADE: We can hear you now, Dr Slater.

DR. SLATER: Okay. Great. Sorry. Just in response to the aspect of following up, these patients

are on a follow up schedule based on their esophageal atresia. If they've undergone surgical repair, that is extremely similar to the follow up that would be required for this study. I think that in the consent it is stated that the follow up is required for the study. That might be something that could potentially be a barrier, but I haven't seen that to be a problem in my experience or people that I've heard from.

DR. HOEHN: Thank you.

DR. WADE: Kelly Wade here. The next clarifying question -- we have two remaining -- will be from Dr. Lukish. You're unmuted, Dr. Lukish.

DR. LUKISH: Thank you, Kelly. Thank you, Kelly. Mark and Ted, nice presentations. I don't know who should field this question or who would know the answer to this. So I think it's important for the group of us to understand that it sounds like the device is safe. It's safe because it has zero mortality, and you got about somewhere between a 3 and 5 percent mortality with open operative. So you have zero mortality. The devastating complication of leak

you have in one kid.

Now tell me that you stated that the leak occurred, and that was attributed to the device being used outside of specifications. Can you articulate exactly what that leak and how that was outside the specifications? I'm just trying to clarify because I think safety and efficacy are two different pieces. And I am okay with FDA approval in a safe device, which I think this is, because the two most important complications death and leak -- leak being extremely rare, one out of, I guess, your 20. But I want to know about that patient who had the leak.

DR. HEISE: So this is Ted Heise. I can take the first stab, and then Mark can add anything needed. I completely agree with your characterization of the benefit-risk calculus. The leak occurred with use of the PEG tube advanced up into the distal end of the lower pouch. The labeling recommendations are for that PEG tube to be secured with a balloon against the inner wall of the stomach. The physician had elected to advance it up into the pouch to increase the leverage,

if you will, on that magnet in the gastric pouch.

DR. LUKISH: So in the surgical world we would call that a technical failure that was a physician judgement thing. Okay. So used within specification if the device is used within specification, there are no deaths, and really, if you exclude that technical failure, there are no leaks. Stricture is very common, probably 30 percent of the kids maybe 40 percent is a more realistic if it's open. But I think it's important for all of us to recognize using this device -- because you haven't -- no child has passed away from its use. And really no child has really developed a leak from the proper use of it. All that can happen is it doesn't work. And if it doesn't work, it doesn't preclude the open or conventional repair.

My only last piece of insight that I want to give -- and I know the day's been late -- but I still am focused on what the device is ideally designed for. And it's ideally designed for the Type A atresia, which is extremely rare, one in 60- or 80,000 live births. When you're utilizing the device in the Type C, it's

going to be very difficult to be able to give us a really important -- data that is really going to prove efficacy because those two patient populations are very different. They're different in when you're using the Flourish, age and time and weight. And they're different in terms of what is the true gap distance. That's the one piece -- so patient population.

And then second piece -- and I'll leave this insight with you -- is I think going forward you have to define -- to the institutions that are participating in the trial, you have to define very carefully how the gap width is being determined because there are many different ways to do it. And some are going to give you a narrow gap width that is likely not accurate. Thank you.

DR. HEISE: So a point taken -- this is Ted Heise -- point taken on the type of atresia. We're certainly collecting that. It is approved for use with various types, including presence of fistulas if they've been repaired prior to use of the Flourish. And I suspect you're right that, even if that fistula's

been repaired, those may be more challenging cases to achieve anastomosis. But I'm hopeful that at some point we may have enough data to be able to sort that out. Regarding the -- what was the second part? That one had an easy answer, and I forgot it.

DR. LUKISH: Determining the gap width -- precisely determining the gap width.

DR. HEISE: Yes. And that's part of the reason that we have a representative at each case to just double check that it really is a suitable candidate.

DR. WADE: Thank you, everyone. Kelly Wade. We're going to have to move forward and go into the voting session. We're going to lose our conference time, and I want to make sure we get a vote documented on this important topic of Flourish. I want to thank the presenters, both from the FDA and the sponsors, for bringing us all this information today.

We've acknowledged this is an incredibly small patient population. But the Flourish device is especially amenable to Type A with esophageal atresia

without the TE fistula component or Type C. But in those cases, the fistula would already have been repaired surgically. So this is a difficult patient population and a device that is uniquely available for these babies.

The voting slide is up. The question, the FDA will report on the following to the PAC in one year's time, 2021: annual distribution number, the PAS follow-up results including the revisions of the PAS study, which is ongoing work between the FDA and Cook, the literature review, and the device review. So does the Committee agree with the FDA's plan for continued surveillance of the Flourish device?

And I do not believe that we will have time for further discussion. But I think we have had a robust discussion and lots of information provided. So let's move forward with our voting. Again, as before today, you should have received an email from the pediatricadvisorycommittee_vote with voting instructions.

The instruction again is to Reply All and when

responding, type your vote "yes," "no," or "abstain" in the body of the email and nothing else. If you encounter technical difficulties as before, please email your assigned POC. We will now start voting on the Flourish question, and you will have 60 seconds to respond to the voting question.

(Pause)

This is our one-minute notification that voting will close. Respond immediately if you have not already done so. We will take the shortest break possible while the FDA compiles the votes and return when the votes will be available to be displayed.

[BREAK]

DR. WADE: Kelly Wade here. We are missing one vote. If everyone could make sure that they submitted their vote, we need those to complete the tally.

DR. WADE: Welcome back and thank you -- this is Kelly Wade. Thank you very much for your patience. Now that the vote is complete our Designated Federal Office will read the record from the screen. Go ahead, Marieann.

MS. BRILL: Hi, Kelly.

DR. WADE: I can hear you.

MS. BRILL: Okay. So this is Marieann Brill. We have -- that is the incorrect slide. I need to send this other slide.

DR. WADE: Oh. Patience, everyone. We've actually been doing really great today given that we've never done this virtually before.

(Pause)

As soon as the slide comes up, we will read the votes. Thank you, everyone, for your patience. If you could, I do need people to stay on the line to read their vote into the record.

(Pause)

Here it is. Thank you again to our audio/visual team and all the FDA supports for this virtual voting process. Go ahead, Marieann.

MS. BRILL: So for Flourish, for the record the voting results are 20 "yes" and two "no" votes, again, 20 "yes," two "no" votes. Thank you.

DR. WADE: Now that the vote is complete we

will go down the meeting roster as we've done before and have everyone who voted state their name, their vote, and, if you want, you can state the reason why you voted as you did into the record. Again, we will start at the top with Dr. Anne.

DR. ANNE: Premchand Anne. I voted yes.

DR. CALLAHAN: David Callahan. I voted yes.

DR. CUNNINGHAM: Melody Cunningham. I voted yes.

DR. CZAJA: Angela Czaja. I voted yes.

DR. DRACKER: Bob Dracker. I voted yes.

DR. FISCHER: Gwen Fischer. I voted yes.

DR. FLICK: Randall Flick. I voted yes.

DR. HAVENS: Peter Havens. I voted yes.

DR. HOEHN: Sarah Hoehn. I voted yes.

DR. HOLUBKOV: Rich Holubkov. I voted yes.

DR. B. JONES: Bridgette Jones. I voted yes.

DR. O. JONES: Olcay Jones voted yes.

DR. LUKISH: Jeffrey Lukish. I voted yes.

DR. McGOUGH: Jim McGough. I voted yes.

DR. McMILLAN: Gigi McMillan. I voted yes.

DR. ORTIZ-AGUAYO: Roberto Ortiz. I voted yes.

MS. OSTER: Randi Oster. I voted yes.

DR. WADE: Jennifer Plumb is next on the list. You may be muted. It looks like you're unmuted, Jennifer. Go ahead.

DR. PLUMB: There it goes. This is Jennifer Plumb. I voted yes.

DR. WADE: Thank you.

DR. SAYEJ: Wael Sayej. I voted yes.

DR. WADE: And Dr. Turer --

(Pause)

DR. McCUNE: Dr. Wade, this is Suzie McCune. I'm not hearing you if you're speaking.

DR. WADE: Thank you. Dr. Turer, if you're on the line, we just need you to read your vote into the record.

DR. TURER: Yes. this is Dr. Turer. I was waiting for the gentleman before me. My vote is yes.

DR. WADE: Thank you very much. As we close out this meeting, I personally would just like to thank

the Pediatric Advisory Committee, our audio/visual team, members of the FDA, and the Cook sponsor team who brought an incredible amount of information to us today. I want to particularly acknowledge the patience we all exhibited in a virtual setting yet still remaining incredibly engaged and providing very thoughtful comments on all the various products and the device that we discussed today. I'd like to turn it over to Dr. Suzie McCune for some closing remarks.

DR. McCUNE: Thank you, Dr. Wade. I was asked actually part way through the meeting today because of some network issues to just make sure that I repeated the vote into the record for all of the votes today. So I just FDA had asked a question about recommending continued routine, ongoing post-market safety monitoring for four drugs. The first was Vyvanse and the vote was 21 "yes," one "no" for Vyvanse. For Mydayis, it was 20 "yes" and two "no." For Adzenys, it was 20 "yes" and two "no." For the discussion of Orencia, which was also routine, ongoing post-market safety monitoring, it was 21 "yes" and one "abstain."

With respect to Gamunex, the question was that we would return to routine safety monitoring, close monitor of all reports of hypersensitivity including lot-specific analyses and continued discussion with manufacturing to further investigate root cause and the vote on that was 21 "yes" and one "no." And the Flourish discussion was that FDA would report on the following to the PAC in 2021: annual distribution number, PAS follow up results, revised PAS study where FDA working in collaboration with Cook, the literature review, MDR review. And the vote on that was 20 "yes" and two PAC members that were unable to stay till the end of the meeting, and so they were not able to vote.

So thank you for letting me read that back into the record. And I just want to thank everyone, especially Marieann Brill, Shivana Srivastava (Inaudible). Sorry. Sheila Reese, Ester Hatton, Margaret Caulk, Marianne Noone, Jonathan Midura, Dionna Green, all of the A/V folks that helped us today, especially when everything went away at 5:00. Thank you so much.

I know that we went over. But because a number of advisory committees have gone over because of technical challenges and actually we went over today because of a really robust discussion. So I really want to thank the PAC members and all of the members from the FDA for a very robust discussion and for helping us with a number of these products today. So thank you very much. And I just want to turn it back over to Dr Wade.

ADJOURNMENT

DR. WADE: Thank you. So I know we're running over today, but I want to just say great conversation today, wonderful patience, and my main concluding remark was that we saw, really, the importance today of safety surveillance for pediatric medications and devices and even the example of a pediatric safety review leading to a discovery of a safety event problem that was primarily seen in adults. So I think the importance of pediatric safety reviews was highlighted today. And the insight that this Committee continues

to provide is very valuable.

So with that I wish you all a good evening. I thank you for your patience today and I thank again, really, the members of the FDA and our audio/visual team who provided so much work today. We really appreciate it. Thank you, everyone. This concludes the September 15th meeting of the Pediatric Advisory Committee.

[MEETING ADJOURNED]