

UNITED STATES FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE MEETING

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Thursday, March 14, 2012

Sheraton Silver Spring

8777 Georgia Avenue

Silver Spring, Maryland 20910

The meeting was convened at 8:00 a.m.,

KENNETH TOWBIN, M.D, Chairman, presiding.

MEMBERS PRESENT: KENNETH TOWBIN, M.D., CHAIRMAN, PRESIDING

VICTOR SANTANA, M.D.

JEFFREY WAGENER, M.D.

GEOFFREY ROSENTHAL, M.D., PH.D.

MICHAEL D. REED, PHARM.D, F.C.C.P., F.C.P.

PHILIP LARUSSA, M.D.

SUSAN BAKER, M.D., PH.D.

JONATHAN MINK, M.D.

MARK HUDAK, M.D.

∞BRIDGETTE WIEFLING, M.D.

† AMY CELENTO, B.S.

CONSULTANTS

MICHAEL WHITE, M.D., PH.D.

JAMES MCGOUGH, M.D.

CHARLES M. GLASIER, M.D.

#SAMUEL D. MALDONADO, M.D., M.P.H., FAAP

ISRAEL FRANCO, MD.

AVITAL CNAAN, PH.D.

ROBERT DRACKER, M.D., MHA, MBA, CPI

GEOFFREY ROSENTHAL, M.D., PH.D.

MARY CATALETTO, M.D., FAAP

ALSO PRESENT: WALTER ELLENBERG, Ph.D.,

Executive Director and Designated Federal Official

Industry Representative
† Acting Patient-Family Representative
∞ Acting Consumer Representative

P R O C E E D I N G S

(8:00 a.m.)

WELCOME AND INTRODUCTORY REMARKS

CHAIRMAN TOWBIN: Well, good morning. I think that we're ready to begin. I'd like to start by welcoming everyone to this meeting of the Pediatric Advisory Committee. I know each of you have many responsibilities, and I am exceedingly grateful to you for your willingness to come here and provide this advisory function to the FDA. I'd like to begin with people going around and just saying who they are and, you know, just a bit about where they're from or their specialty. Why don't we start with Dr. Maldonado and we'll just go around counter-clockwise.

DR. MALDONADO: Sam Maldonado. I represent industry in this advisory committee, and also pediatrician.

MS. CELENTO: Amy Celento, the patient representative.

DR. WIEFLING: Dr. Bridgette Wiefeling. I'm Med-Peds, Rochester, and advocate.

DR. WAGENER: Jeff Wagener, Pediatric Pulmonary University, Colorado.

DR. GLASIER: Charles Glasier. I'm a pediatric neuroradiologist from the University of Arkansas and Arkansas Children's Hospital in Little Rock.

DR. FRANCO: Israel Franco, pediatric neurologist from New York Medical College in New York.

DR. DRACKER: I'm Bob Dracker; pediatrics, hematology, and transfusion medicine; Syracuse, New York.

DR. LARUSSA: Phil LaRussa, pediatric infectious diseases, Columbia University, New York.

DR. CATALETTO: Mary Cataletto, pediatric pulmonology, Winthrop University Hospital.

DR. HUDAK: Mark Hudak, neonatologist, University of Florida College of Medicine, Jacksonville.

DR. BAKER: Susan Baker, pediatric nutrition and gastroenterology from Buffalo, New York.

DR. WHITE: Michael White, pediatric cardiologist and chair of our IRB at the Ochsner Health System, New Orleans.

DR. ROSENTHAL: Good morning, Geoff Rosenthal. I'm a pediatric cardiologist at the University of Maryland.

DR. MCGOUGH: Jim McGough, child and adolescence psychiatrist from UCLA.

CHAIRMAN TOWBIN: I'm Kenneth Towbin. I'm a child and adolescence psychiatrist at the National Institute of Mental Health in the Intramural Research Program.

DR. ELLENBERG: Good morning. I'm Walter Ellenberg. I'm the designated federal official in the Office of Pediatric Therapeutics at FDA.

DR. SANTANA: Good morning. I'm Victor Santana. I'm a pediatric oncologist from St. Jude Children's Research Hospital in Memphis, Tennessee, in the University of Tennessee Health Science System.

DR. REED: Good morning, I'm Michael Reed. I'm a pediatric clinical pharmacologist and toxicologist at Akron Children's Hospital and at Northeast Ohio Medical University.

DR. MINK: My name is Jonathan Mink. I'm a pediatric neurologist from the University of Rochester.

DR. CNAAN: Avital Cnaan. I'm a biostatistician in Children's National Medical Center and George Washington University.

DR. COPE: Judy Cope. I'm a pediatrician; head up the safety team for the Office of Pediatric Therapeutics at FDA.

DR. YAO: Lynne Yao. I'm a pediatric nephrologist and the associate director of the Pediatric and Maternal Health Staff at FDA.

DR. MURPHY: Dianne Murphy, pediatric infectious disease background, and I'm the director of the Office of Pediatrics Therapeutics at the FDA.

DR. HAUSMAN: Ethan Hausman; pathology, pediatrics, transfusion medicine. I'm a reviewer in the Office of Surveillance and Epidemiology Pharmacovigilance.

DR. MARTIN: I'm David Martin. I'm the Director of the Division of Epidemiology at the Center for Biologics -- that's the postmarketing safety division -- and I'm an occupational medicine physician.

CHAIRMAN TOWBIN: Thank you all very much. Just a couple of things before I turn things over to Dr. Ellenberg. I just want to remind people that when you speak into the microphone, if you'll say who you are, that will help with our documentation quite a bit. And if you'll remember to turn your microphone off when you're done, that will prevent feedback in the system and other kinds of minor difficulties. So I think with that, Dr. Ellenberg has some introductory remarks.

DR. ELLENBERG: Good morning, everybody. I need to read the following statement as we begin the meeting today. Again, good morning to the members of the Pediatric Advisory Committee, members of the public, and FDA staff. Welcome to the meeting, and we appreciate you attending this early in the morning. The following announcement addresses the conflict -- excuse me -- addresses the issues of conflict of interests with regards to today's discussion of reports by the agency as mandated by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Based on the submitted agenda for the meeting and all financial interests that have been reported by the committee participants, it has been determined

that those individuals who will be participating in each topic do not have a conflict of interest for the following products. The products are: Menactra, Hizentra, Alimta, Gadavist, Kedbumin, Natroba, Moxeza, Kytril injection, Nexium, Nexium IV, INOmax, nitrous oxide, Actemra, Lamictal, Invega. In addition, several products will be presented during the abbreviated products section of the meeting.

At the appropriate time, which will be approximately 9:45 this morning, designated members of the Pediatric Advisory Committee who have been screened for potential conflicts of interest will present the following products to the FDA, but there will be no discussion. The designated abbreviated reviewed products for today's meeting are: Uroxatral, Creon, and Zenpep. In order to provide the expertise required to adequately address all of the products covered at today's meeting, the following expert consultants will be participating as temporary voting members: Dr. White, Dr. Cataletto, Dr. Dracker, Dr. Rosenthal, Dr. Glasier, Dr. Franco, Dr. Cnaan, and Dr. McGough. I'd also like to point out that today Dr. Bridgette Wiefeling is participating as the consumer representative, which is a voting position on the committee. Ms. Amy Celento is participating as the patient family representative, which is also a voting position.

In general, the committee participants are aware of the need to exclude themselves from involvement in the discussion of topics if their interests would be affected, and their exclusion will be noted for the record. Therefore, we'd like to note the following recusals for today's meeting: Dr. Dracker will step away from the table and be recused from the discussion of Menactra; Dr. Cnaan will step away from the table and be recused from the discussion of INOmax; Dr. Reed will step away from the table for several products, which are Lamictal, Actemra, Hizentra, Menactra, Nexium, and Nexium IV. We will remind each of you at the time of we need to cover each individual product that you need to step away from the table.

I'd also like to point out that Dr. Samuel Maldonado will serve as the designated acting industry representative. The industry representative is a non-voting member of the committee; however, is not a special government employee. The industry representative represents all interested persons within the class of industry interests and does not represent any particular organization or group. If a matter before the committee that directly or indirectly affects the company employing the individual exists, then the member shall inform the committee, but need not be absent during the discussion or decline to participate in the discussion; however, may not discuss the company's position on the matter, and that's per 21

CFR Section 14.86 C4. However, to illuminate any perceived conflicts, Dr. Maldonado has informed us that he will not participate in matters involving Invega. There is one waiver that we issued for this meeting. Pursuant to 18 USC 208B(3), Dr. McGough has been granted a waiver to participate in the discussion of Invega. The information regarding his waiver is available on the Pediatric Advisory Committee website.

With respect to all other participants, we ask that in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment on. We have one open public session, which is scheduled to begin at approximately 11:30 this morning. Copies of the material that were presented as comments to the open public session are available outside in a three-ring binder on the registration table, and they will also be available online.

For the members of the committee, just to remind you, please turn your microphones on when you speak. Due to the acoustics in the room, try to speak up loudly so that we can capture everything you say, and then turn your mikes off at the conclusion of your statement. I want to also remind the committee members and the audience to please silence your Blackberries, cell phones, and any other electronical devices so they avoid interrupting the meeting. And at this time I'd like

to turn it to Dr. Murphy to see if she has any introductory remarks.

AGENDA OVERVIEW

DR. MURPHY: Very briefly, as always, thank you sincerely for coming and taking time to participate in this safety review. Again, this is a different process than many FDA advisory committees in that we try to cover an enormous number of products, otherwise we'd have to meet almost every day. So you have been tasked with reviewing 17 products -- well, there're really 16 products and one is in two forms -- and we have developed, with your help, a number of abbreviated processes. Today we are going to present another one to you. The Center for Biologics feels that, after looking at what the committee's been able to do, again, trying to get at the whole objective of this review, is to let the committee focus on things that might warrant discussion and not spend a lot of time on things that have, you know, nothing new, interesting, or, even though there's nothing new or interesting, we still want you to discuss them, but for those that there's absolutely nothing by criteria developed, we have developed these abbreviated processes. And I know they're getting to be -- I think we're on our fourth type of abbreviated. So don't worry about which type it is, and we'll be glad to help you if there are any questions as we go through today, because you're going

to go through, I think, almost all four types of abbreviated today.

We welcome your feedback on this. Actually we seek your feedback on this, because we are being asked, because of the continuing issue with resources, to develop more and more efficiencies and to do things, you know, more effectively, and we'll actually be coming back to the committee and talking about even doing one meeting possibly a year remotely. I mean, we are really trying to develop alternative ways. However, we don't want to endanger the discussion, because that's why we bring you here. But I just wanted to give you a heads up that you may be hearing from us about other ways to -- well, let's put it this way: we'd like you to experiment with us. We may be piloting some new studies on how to do advisory committees, so don't be surprised if we come and ask you that.

I also want to congratulate you. You've made it through conflict of interests to get here [laughs]. We have to -- we have a challenge at every meeting trying to get through the conflict of interest for all of the specialties, and you will hear today we've had the area of rheumatology -- pediatric rheumatology. After going through almost a dozen individuals, we were not able to get anybody through the process, and so we have asked someone to present to you. I bring this up only because in the situation, this is an expert who we want you to

be able to ask questions about the expertise, but she cannot sit at the table; she cannot vote. She's here to be a resource for you, and we've asked her to present before that discussion.

And I will stop at that point and let us get on with the meeting. Thank you.

DR. ELLENBERG: Very well [clears throat]. Pardon me. So, with that, I think that we're ready to begin our discussion of Menactra.

So, just by way of introduction, Dr. Baer is a medical officer in the Division of Epidemiology at the FDA's Center for Biologics Evaluation and Research. She attended medical school at the Johns Hopkins University School of Medicine and completed her pediatrics residency at the University of Colorado, the Children's Hospital of Denver. Prior to joining CBER in 2012, Dr. Baer practiced clinical medicine as a pediatric hospitalist. Welcome, Dr. Baer.

MENACTRA MENINGOCOCCAL (GROUPS A, C, Y, AND W-135)
POLYSACCHARIDE DIPHTHERIA TOXOID CONJUGATE VACCINE)

DR. BAER: Thank you. Good morning. This is the Menactra Post-licensure Pediatric Safety and Adverse Event review. Menactra is a meningococcal conjugate vaccine that was approved for active immunization to prevent invasive meningococcal disease caused by serogroups A, C, Y, and W-135. The objectives of this PAC review is to first of all look at the background information for Menactra. This will include the timeline and also address Guillain-Barré syndrome as an early safety concern. We will then look at safety-related label changes during the PAC review period and the incorporation of postmarketing study results in the label. We will then look at adverse event review with reports to the U.S. VAERS with vaccination dates April 22nd, 2011, through April 22nd, 2012. Finally, we will review the pharmacovigilance plan and the status of postmarketing safety studies.

Menactra was first approved for use in the United States in 2005, originally for the ages 11 to 55 years old. There have been two expansions of the age indication since that time. The first was in 2007 and it included ages 2 through 10 years old. The second expansion was on April 22nd in 2011, to include ages 9 through 23 months old. The second age expansion

was the trigger for this PAC one-year review. Prior to that expansion, over 41 million doses were distributed in the United States. The sponsor estimates that approximately 70 percent of doses were for use in under-16-year-olds. During this one-year review period for the PAC, just under 8 million doses were distributed in the United States. The sponsor estimates that approximately 66 percent of those doses were for use in less-than-16-year-olds and .06 percent, or approximately 5,000 doses, were for use in the new age range of 9 through 23 months.

When Menactra was first licensed in the United States in 2005, that was also its international birthdate; it is now approved in over 30 countries. The Advisory Committee on Immunization Practices, or ACIP, recommends routine vaccination at age 11 or 12 years old, with a booster dose at age 16 years old. It also recommends vaccination for high-risk individuals age 9 months to 54 years old.

Shortly after licensure, there was a concern for GBS as a potential early safety signal. Guillain-Barré syndrome, or GBS, is an acute neurologic disorder involving inflammatory demyelination of the peripheral nerves. There were five reports of GBS following Menactra made to VAERS in the first seven months of 2005 following Menactra's licensure. All of these cases involve 17- and 18-year-olds who have been vaccinated 14 to 31 days prior to symptom onset. This rare and serious event

being reported led to the development of two large postmarketing studies.

The first study was held in the Vaccine Safety Datalink. This allowed real-time surveillance of over 800,000 doses in eight managed care organizations. These doses were administered to 11- to 19-year-olds from the years 2005 to 2010. In this study there were five potential cases of GBS in the one-to-42 day risk window that were then reviewed on chart review. Two of these five cases had preexisting diagnoses of GBS; one had a diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy, not GBS; one case was a rule-out GBS that had a different, unspecified final diagnosis; and the final case had symptom onset on day zero. Therefore, there were no confirmed cases of GBS in the one-to-42 day risk window following Menactra vaccination.

The second large postmarketing study was sponsored by Sanofi Pasteur and conducted by Harvard Medical School and Harvard Pilgrim Health. This was a retrospective cohort study in a large linked health care database which included 9.5 million patients aged 11 to 18 years old from the years 2005 to 2008. 1.4 million doses, or 15 percent of the patients, had received Menactra. There were 18 potential cases of GBS in the 42-day risk window following vaccination. On chart review, nine of these cases were ruled out as not being true GBS. The

remaining nine cases had insufficient chart information for determination. Using a case confirmation rate of 27 percent from all potential GBS cases in this study, it was determined that there could be up to three additional cases possible of GBS. Taking into account this missing information, the attributable risk of GBS from Menactra ranged from 0 to 5 additional cases per 1 million vaccinees within the six-week period following vaccination. These results from this postmarketing study were included in the Menactra PAC product insert with an update in the Warnings and Precautions section and the Adverse Reactions section in November of 2011.

The second safety labeling change that occurred during this one-year review period was that the possibility of latex allergic reaction was removed from the Warnings and Precautions section as the manufacture had changed the type of vial stopper being used so that it no longer contained latex.

Looking at the adverse events reported to VAERS with vaccination dates of April 22nd, 2011, to April 22nd, 2012, across the top of the chart are the serious cases, the fatal cases, non-serious, and total. The rows are divided by the different age groups. Globally, there were 1,118 reports. All but seven of those reports were from the United States. The vast majority were non-serious reports. Highlighted in blue is the new age range of 9 to 23 months. As you can see, there was

only one non-serious report in this age group. It was a 13-month-old male who developed a generalized rash and fever nine days following multiple vaccinations. Highlighted in yellow are the remaining pediatric age group, 2- through 16-year-olds. There were 39 U.S. serious cases in this age group and two fatal cases. We will review those in more detail.

The two pediatric fatal cases reported to VAERS during this one-year review included an 11-year-old female with a history of Rett's Syndrome who died of aspiration and associated cardiorespiratory arrest four days after vaccination. The second case was a 15-year-old male with pervasive developmental disorder and epilepsy who died of an apparent epileptiform seizure three days after vaccination. He had received concomitant vaccination with Tdap and HPV. There was no pattern identified among these death reports.

The 39 serious U.S. reports in 0- through 16-year-olds -- just as a reminder, there were no cases of serious reports under 2 years old -- there were six hypersensitivity reactions, five cases of cellulitis, four cases of Syncope, two cases each of GBS, Transverse Myelitis, nausea, dizziness, and Type 1 diabetes mellitus. There were six cases of single diagnoses in the neurologic category and 10 cases of single diagnoses that were non-neurologic. There were four cases of GBS reported for all ages during this one-year review period. Considering the

distribution data, that leads to a reporting rate of 0.5 per million doses. This is consistent with the GBS safety information in the package insert.

Considering the non-serious U.S. reports in 0- through 16-year-olds, these are the top 10 preferred terms for those reports. Six of the 10 are localized injection site reaction, such as erythema or swelling. The four remaining preferred terms were dizziness, Syncope, pyrexia, and headache. All 10 of these preferred terms are listed in the product insert.

The Sanofi Pasteur pharmacovigilance plan includes routine pharmacovigilance for serious and unexpected events. There are two ongoing postmarketing commitments, or PMCs, for the previously approved age ranges of 11 to 55 years old and 2 to 10 years old. There are also two PMCs for the new age range of 9 to 23 months old.

The first postmarketing commitment in 11 to 55 years old is a retrospective observational safety study conducted in the population of Kaiser Permanente, Northern California. This study has evaluated 30,000 doses; 94 percent of those were in the age range of 11 to 18 years old. The study includes two analyses. The first is a self-controlled cohort analysis comparing the risk interval 0 to 30 days after vaccination, with a control interval 31 to 60 days after vaccination. The second analysis is a matched cohort design with a historical control

with a six-month follow-up period. The end points for this study are all ER visits and hospitalizations and outpatient visits for specified neurological conditions, hypersensitivity reactions, and new onset autoimmune diseases.

There was no formal hypothesis tested in this study. 1,660 comparisons were made by diagnostic code, age, and setting. There was no adjustment made for multiple comparisons. So, assuming an alpha of .05, by chance alone there would be 83 statistically significant findings expected. The preliminary results are all that we have available at this time. They were provided to us by the manufacturer in a poster presentation. They showed 21, or 1.3 percent, of the comparisons between the risk and control intervals were significantly elevated, and 44, or 2.7, were significantly decreased in the risk interval.

The preliminary results for the short-term follow-up of 0 to 60 days showed automated results that had increased rates of abdominal pain, febrile illness, and suicidal ideation and attempt on days 0 through 30 versus 31 through 60 post-vaccination. These three terms were then followed up with in-depth chart review. For abdominal pain, there were multiple different diagnoses found and there was no clinical pattern identified. For suicidal ideation and attempt, all of the patients had risk factors prior to vaccination, including prior

attempts, depression, stressors, and alcohol abuse. And for febrile illness, the chart review is still in progress.

For the longer term six-month follow-up, there were 11 diagnostic codes that had elevated rates in the six-month post-vaccination period. On further review of these cases, many had onset prior to vaccination. There was no temporal clustering within the six-month period and there were no clinical patterns identified. The authors therefore concluded that there are no serious new safety concerns from this preliminary data analysis. There were also no cases of Guillain-Barré syndrome in vaccinated patients. We are awaiting the final study results, which are expected in 2014.

The second postmarketing commitment is a study in 2 to 10 years old. This is an observational safety surveillance study in the Kaiser Permanente Medical Care Program population. This study has a stage one, which is three years of duration or approximately 2,000 patients, and a stage two that would only go into effect at the time of routine recommendation by ACIP for vaccination in this age group. It would then continue to 20,000 patients. This study has a self-controlled analysis with a risk window at 0 through 30 days post-vaccination and monitoring up to six months. Once again, the safety endpoints are all ER visits and hospitalizations and outpatient visits for specified neurological conditions, hypersensitivity reactions, and new

onset autoimmune diseases. This study was started in July of 2008. Stage one is complete and we are awaiting those results.

The third postmarketing commitment is a study in the new age range of 9 to 23 months old. This is a phase four self-controlled epidemiological safety surveillance study of the two-dose schedule in children 9 to 23 months old. The population is Kaiser Permanente, Northern California. This study also had two stages. The first stage would include 3,000 patients or three years, and stage two would only go into effect at the time of an ACIP recommendation for routine vaccination in this age group. It would then continue until 20,000 patients. The safety endpoints are all ER visits and hospitalizations and outpatient visits for specified neurologic conditions, hypersensitivity reactions, and new onset autoimmune diseases. The rates of events in days 0 through 30 post-vaccination versus days 31 to 75 post-vaccination are compared in a self-controlled cohort. This study is projected to be completed in December of 2014.

The final study is a concomitant vaccine open-label study in children 9 through 18 months of age. This is a parallel group study to evaluate the safety and immunogenicity of two doses of Menactra given alone at nine months and concomitantly with Pentacel at 15 to 18 months of age. The study is to include 1,300 patients from multiple sites that will look at immediate adverse events, and then adverse events within

seven days and 30 post vaccination. The study is scheduled to be completed in June of 2014. The FDA pharmacovigilance plan is to continue passive surveillance using VAERS, and to follow up on the results of the Sanofi Pasteur post marketing safety studies. In summary, GBS was evaluated in the vaccine safety data link and in a second large post-marketing study. Over 2.3 million doses were monitored and there were no confirmed cases of GBS in the risk window of 1 to 42 days following Menactra vaccination. There were no new safety concerns identified during this one-year review period. The Menactra package label adequately reflects the known safety profile. FDA recommends to continue routine monitoring for new safety signals in VAERS and follow up on results of the post-marketing studies. Does the advisory committee concur?

CHAIRMAN TOWBIN: Thank you very much, Dr. Baer. Just before we begin with questions and comments, I wanted to point out that Dr. Dracker has removed himself from the table. Dr. Reed also is recused from the discussion of Menactra. And so, if we could begin with questions, comments people have. Dr. LaRussa.

DR. LARUSSA: So let's see, this is Slide 18. Can you just give us a little more information on the suicidal ideation attempt? It sounded like you were saying everybody had risk factors, but that there was -- there were increased events in

the zero-to-30-day window as opposed to 31-to-60. So, just tell us a little more about that.

DR. BAER: Absolutely. So once again, these are preliminary results and we have very limited information, so we are awaiting those final study results. There were six cases in the zero-to-30-day risk window, compared to zero in the control window. Five of those six cases had charts that were available for review. So the actual number of cases was very small considering the study of 30,000 patients. Three of the cases were suicidal ideation and three of the cases were suicidal attempt. All five of the patients had significant risk factors that predated the vaccination. So things to take into consideration when looking at this is the very high rate of suicidal ideation and attempt in this age range already. The CDC risk youth behavior survey each year has shown a rate of 6.3 to 8.8 percent for suicidal attempts in the one year previous for the 9-to-12th-grade age group. The numbers in the study were considered to be relatively small. We have also followed this on passive surveillance. We have 10 reports in the seven years that Menactra was on the market for any suicidal attempt or ideation. So, we will review the final study results when those become available to us.

CHAIRMAN TOWBIN: Yes, Dr. Santana.

DR. SANTANA: So, can you go to Slide 21?

DR. BAER: Sure.

DR. SANTANA: So you told us earlier that in the first year since the expansion for the infant group, the 9-to-23 months, 5,000 doses were distributed, and I understand the issues with doses versus patients, but that's not the question. The question is how likely, then, is that this study on Slide 21 can be completed by December 14th, before Stage 2? You're looking for 20,000 patients. Isn't that really a very high bar, given the fact that in the first year of the expansion only 5,000 doses were distributed?

DR. BAER: So, Stage 2 is set up to only go into effect if there is an ACIP recommendation for routine vaccination with a meningococcal conjugate vaccine in this age group.

DR. SANTANA: So, the December 14th is really for the Stage 1 timetable.

DR. BAER: Yes.

DR. SANTANA: Okay.

CHAIRMAN TOWBIN: Are there any other comments?

LaRussa.

DR. LARUSSA: Just remind me for when you are adjudicating cases of Guillain-Barre, are you using Brighton Level 1 or Brighton Levels 1, 2 -- how are you adjudicating them?

DR. BAER: So the two different studies both used Brighton collaboration definitions, and they did have different categories, and included possible and probable, but there was none determined to be within the risk window a true definition.

DR. LARUSSA: By any Brighton level or Brighton Level 1?

DR. BAER: I am not certain.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: Just a quick question about how Guillain-Barre is approached in general. So do we -- are we smart enough to know the attributes of specific vaccines that are more likely to result in seeing Guillain-Barre in people who received those vaccines or is it really just something that we see sort of sporadically across classes and types of vaccines? And if there is a tendency to see a little more Guillain-Barre in certain types of vaccines -- [clears throat] excuse me -- does this particular vaccine fall into the class where we might be expected to see it or not?

DR. BAER: So Guillain-Barre was historically connected with the 1976 swine flu vaccination, and because of that influenza is always watched -- the influenza vaccines are always watched extremely closely. I am not familiar with patterns of certain types of vaccinations that are known to be linked. I don't know if anyone else has any further comments

from the vaccine department. I don't -- I don't believe so.

CHAIRMAN TOWBIN: Dr. Martin has his light on.

DR. MARTIN: Right, sorry. David Martin from Division of Epidemiology. So I would say that, exactly, if you look at the FDA package and sort of -- so the FDA has acknowledged an attributable risk from season influenza vaccination. Obviously, we have the publications from the swine flu affair as well, but, yes, when the VAERS cluster was found in 2005, that was considered to be, in a sense, a novel safety signal, and really sort of added a new concern regarding meningococcal vaccines to be sort of preexisting concern, which was predominantly focused on flu vaccines.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: So as far as I'm aware, the last time the Institute of Medicine reviewed this subject, although there's general concern about the influenza vaccine category, it's, as was mentioned, only the '76, '77 flu, where there is felt to be adequate evidence to support the causal association with the vaccine.

CHAIRMAN TOWBIN: Dr. Martin.

DR. MARTIN: Just going to respond to you, because I also want to make sure you've got an additional answer to your prior question about Brighton levels. So first of all, right, the issue is that the IOM is doing their review for purposes of

compensation. And so, as you said, they are looking at a higher bar, and, obviously, the FDA is looking at association and observational epidemiologic studies. So that -- so it's not a true inconsistency; it's just there's sort of a one bar for warning providers regarding what's seen in the observational literature, and there's quite another bar for determining compensation. So that's essentially a HRSA activity rather than an FDA activity. The -- In this case with Menactra, both of those studies, both the VSD study in that case was sponsored by the CDC, and the other study was sponsored by the sponsor, and they worked with academic groups. So again, we can't speak for their -- we'd have to go back to the publications to look at their -- look at their methods, but typically when the FDA executes its own studies like in the prison system, or if we have a post-marketing -- a required post-marketing study, we're in the setting. We're not setting, we're actually, in a sense, dictating the protocol. Then you typically have, you know, an analysis that would have, like, Brighton Level 1, and then potentially a sensitivity analysis with Brighton Level 2. But I think what Dr. Baer was sort of saying to you was that all of the cases did not meet any of those Brighton levels because there were no -- there were no confirmed cases at either of these studies. So essentially, you know, they were all not classifiable, essentially.

CHAIRMAN TOWBIN: All right, well, so perhaps with that, people are ready to approach the question which is do we concur with returning this to its routine monitoring, of course looking toward the results of the post-marketing studies that still remain to be completed. So if we could go around. I think, Ms. Celento, if we can start with you.

MS. CELENTO: Yes, I vote.

DR. WIEFLING: This is Bridgette Wiefeling and I concur with return to routine monitoring.

DR. WAGENER: Jeff Wagener, I agree with returning. And I'd also complement Dr. Baer on her presentation.

DR. GLASIER: Charles Glasier, I concur.

DR. FRANCO: Israel Franco, I concur.

DR. LARUSSA: Phil LaRussa, I agree.

DR. CATALETTO: Mary Cataletto, I agree.

DR. HUDAK: Mark Hudak, I agree, too.

DR. BAKER: Susan Baker, I concur.

DR. WHITE: Michael White, I concur.

DR. ROSENTHAL: Geoff Rosenthal, I agree.

DR. MCGOUGH: Jim McGough, I agree.

DR. SANTANA: Victor Santana, I concur.

DR. MINK: Jon Mink, I concur.

DR. CNAAN: Avital Cnaan, I concur.

CHAIRMAN TOWBIN: So it sounds as if we're unanimous

in our concurrence to return this to routine monitoring, and, of course, we're interested in the results of these post-marketing studies, and I hope to hear about them. I think we're ready now to move on, and we'll hear from Dr. Buch.

DR. MURPHY: I have only one thing to say to the committee. This is probably the last time today you're going to see 21 million of anything, so [laughs] the numbers will progressively go into smaller categories.

CHAIRMAN TOWBIN: Thank you.

MODIFICATION OF CBER PRESENTATIONS
TO THE PEDIATRIC ADVISORY COMMITTEE (PAC)

DR. BUCH: Thanks. Good morning, thank you for indulging me for a few minutes. I'm here basically to remind folks of something that CBER instituted last year as a result of sort of looking back and looking forward at upcoming events, including sequestration and other legislative issues that are before us. So for those of you who have heard this already, I apologize; for those of you who haven't, here we go. I'm just going to talk a little bit about some policy and procedure changes, one of which you've already witnessed this morning. But first let me just tell you that one of the reasons we decided to look at our procedures was we noticed that our presentations to the PAC are increasing, and will be increasing past 2013. And when we looked at them, we looked at whether there were significant recommendations to change, and we realized that there were a lot of CBER products that were recommended for continued safety monitoring, and very few for labeling or other recommendations which attests to, I hope, our ability for post-market review, surveillance, and actions. So our current -- or, well, actually this isn't our current processing anymore; we have changed already since last year. But you will notice today that we did not provide a pre-market

presentation about Menactra. So we've changed and we are now only doing a full safety in use post-market presentation; however, we do still provide full briefing package information and full safety in use in the review memo.

So the current categories, as you know, are standard abbreviated, justified abbreviated with a rationale, and designated abbreviated, and I understand there's a fourth abbreviated that's coming the way. So why did we change? Well, as I mentioned, we looked back at our policy and we wanted to be consistent with other presentations that were already in progress. So we haven't really developed an official written guidance or policy for oral presentations to the PAC, and we thought it was time that we thought about these things. And we also, as always, are trying to make sure that we're using FDA and PAC resources efficiently. Hopefully there's a benefit to the Pediatric Advisory Committee with our change, and particularly in time for -- making time for discussions for significant issues that are ever emerging. And if -- by providing a written policy for our staff, we have a clear guideline for moving forward. So what will not change is our current practice of providing full information to the PAC, as you, hopefully, evidenced in this pre-presentation package. We'll have the same safety in use review, same clinical, pharmacologic, and statistical review, and other information

included in the package for your review prior to the meetings, as well as current labeling.

So our new approach from CBER's point of view is a tiered approach, and we believe that it does not compromise transparency, safety analysis, or reporting, as well -- and/or compliance with the law. We also continue to have CBER expert staff available. You'll see them around the room, should any product specific or product policy issues arise. Our standard presentation will change only in that we will not provide pre-market information, only as appropriate, with a focus on safety, and we will continue to provide the same information that we have previously in the post-market presentation. There is a focus in this presentation on post-market and post-market safety, as you witnessed in the Menactra presentation. We did change the criteria so that we would have a good policy to move forward on this, and these criteria include a new safety signal that is identified by OBE, foreign regulators, or sponsors during pre-licensure, or post-approval surveillance. We will also do a full presentation when FDA is recommending a post-market required study, a REM study, or additional studies that may be appearing in Mini-Sentinel duty, either pre-licensure pharmacovigilance processes or a safety signal. This will also include new changes made in the label as a result of serious adverse events or other surveillance information, and in very

rare cases there may be a case where FDA is requiring a labeling change and the sponsor does not agree.

The justified abbreviated presentation with a rationale is going to be a little bit different for CBER, and the reason is that we do talk about deaths in the abbreviated presentation. And this is usually with new safety signals identified as a result of post-approval or post-licensure surveillance. We know that due to the size of most vaccines, post-market studies in particular, deaths could be anticipated and particularly when a vaccine is universally recommended. We also think that an abbreviated presentation is warranted when no safety signal is resulting in a PMR, a Mini-Sentinel study, or a REM study, and when product labeling has changed for any safety reason other than described in the criteria for a standard presentation. And in this case, this would be when the sponsor and FDA agree. We also think that in this case, when new instructions for use have been added to the label that are not related to safety, that an abbreviated presentation can be used. A standard abbreviated presentation would not result in any oral presentation, as you'll see today, and in these cases the product has little use or is not marketed. There are few, if any, serious adverse events, no deaths, no new safety signals, and product labeling for safety is appropriate. I think that's pretty clear. So the abbreviated slide you'll see today looks

like this, and you will receive all the product information previous to the meeting for your review. Hopefully that was clear. I tried to be quick. Any questions?

CHAIRMAN TOWBIN: You were quick. Thank you very much.
Dr. Santana.

DR. SANTANA: So on Slide 14 -- this is Dr. Santana. On Slide 14 and 15, it looks like the trigger is a new safety signal.

DR. BUCH: Correct.

DR. SANTANA: But how about a signal that's already there or by its frequency, or by its severity has changed? Wouldn't that require some discussion, too? So you know that X happens this number of times; so you know that there's a signal already, it's not a new signal. When all of a sudden your data is showing that it's occurring at a much higher proportion or it's occurring at a much higher severity, wouldn't that also be a trigger for some sort of public discussion by this group? I'm just presenting that as an option, because a new safety signal is really a very high bar. It's something that's really new. But I'm worried about things that already we know but have changed. We look at the data --

DR. BUCH: Right, that would also be within our discussions, and we wouldn't --

DR. SANTANA: So that would be included also?

DR. BUCH: -- obviously we don't ignore those things when those things might trigger other things such as other post-market studies and within the post-market surveillance. So we would definitely bring those to the attention of the group.

DR. SANTANA: So let me follow you. So you are agreeing with that that would trigger some discussion, those scenarios?

DR. BUCH: Yes.

DR. SANTANA: Okay, thanks.

DR. BUCH: It may be that that would go into the abbreviated with justification, depending on whether -- if it's not new. If there's a change in the way that, you know, it would affect labeling or in how we do studies, okay?

CHAIRMAN TOWBIN: There may be a matter of parsing words, but it's possible that an increase in a preexisting signal would be considered a new safety signal.

DR. BUCH: Right. I'd leave that to our OBE colleagues, because they're very diligent about looking at those things every day, you know, they would notice these changes, and probably would bring it to your attention before you knew about it. Okay. David, do you have anything to add?

CHAIRMAN TOWBIN: Dr. Martin.

DR. MARTIN: Right. No, I think we could -- this is sort of just a words sniffing issue. Essentially all safety

signals at some point are new, and I think that just crept into the language, but really the intent is if there's a safety signal, then we'll bring it to the PAC. Likewise, as she said, I guess you could envision an instance where we identified a signal that was once new, say during the pre-licensure process that led to a required post-marketing study, perhaps we return to the PAC and that study, you know, obviously in a sense refuted that safety signal. And then, you know, over the years there might be additional PAC triggers, and if there were no more, sort of, developments regarding that previously, you know, identified safety signal that was not verified in any type of our verification work, say like in the Mini-Sentinel program or the sentinel initiative. Then, obviously, it wouldn't come back to the committee. That, sort of, -- that would be an example where we might not bring it back; we might have like an abbreviated presentation, whereas, obviously, if we engaged in that required post-marketing study, and it were, say, underway, and there were another PAC trigger, and we came back to the committee, we would be updating you and obviously we would be updating you when that required post-marketing study was completed, or when we completed our study using the sentinel initiative. So -- right. So, the intent is clearly to provide what you're seeking, and I think if we just strike the word "new," then I think everybody will be happy.

DR. MURPHY: And I think in prior other processes we have included the word, you know, "new," or "increased severity," or "frequency" that would warrant that type of review.

DR. MARTIN: Right. Well, you're exactly right. I mean, in the legislation that increased FDA's post-marketing safety authority, you know, when we're establishing required post-marketing studies, we can use, you know, and identified risk where there's new -- sort of new information, things of the type that you're describing, concerns about an increased rate for this new risk that may be, you know, you need to better characterized the rate, because you're dealing with, sort of, imperfect surveillance methods on the front end. And that allows us to utilize the sentinel system or to ask for required post-marketing studies. You're exactly right that our underlying authority allows us to engage with those issues and bring those to you.

DR. BUCH: Right. And I would just add -- this is Dr. Buch again, that I completely took the words "frequency" and "rate" out of this sort of discussion, because we really don't have good denominator data. So I was trying to avoid using those terms, but you're correct, "new" in the sense that it's different than what we already know, would certainly be a viable interpretation.

CHAIRMAN TOWBIN: Other comments? All right. Dr. Buch, I apologize that I didn't introduce you properly.

DR. BUCH: No, it's fine.

CHAIRMAN TOWBIN: I appreciate your indulgence.

DR. BUCH: No problem.

CBER JUSTIFIED ABBREVIATED PRESENTATION --
HIZENTRA GLOBULIN SUBCUTANEOUS (HUMAN) 20% LIQUID

CHAIRMAN TOWBIN: All right. Well, so with that, I think that we're ready to move on. Dr. Cope is going to tell us about Hizentra.

DR. COPE: Let me get the first slides up.

CHAIRMAN TOWBIN: Dr. Cope. I guess I have a very nice introduction. So Dr. Cope has been with the FDA since 2003, working first with the Center of Devices and Radiological Health on pediatric device related issues, and then with the Office of Pediatric Therapeutics to focus on pediatric safety for FDA regulated products. Her clinical background is in adolescent medicine, general pediatrics, and epidemiology; and then after several years of clinical and academic practice, she received a master's in public health, in epidemiology and biostatistics. Dr. Cope.

DR. COPE: Thank you. Good morning. Actually, following Dr. Buch's talk, I just thought I would open it up and tell you today, and highlight that this is actually the 25th meeting for the PAC. So the PAC meetings go back to 2003 and we've had well over 200 products undergo the mandated pediatric safety reporting, and with that the process has been evolving, as others have said this morning, with the abbreviated type

presentations, and last year you may remember we started with the designated abbreviated review process. And that it really has been very successful thus far, really, in reducing the workload of everybody, decreasing the conflict of interest clearances that have to go on, the presentations, and also the number of preparation meetings that go on. But importantly, it's really allowed you, the PAC, to focus on those safety issues that really seem to be important with certain drug products that come before us, and really that deserve your attention, and not spend really the undue time on products that are unlikely to have safety concerns. So with that, I'm just going to open it. Now, we're going to cover five different abbreviated presentations there. So five products have been chosen to go under the abbreviated presentations. I'm going to sort of jump around a little bit, but try and guide you. We're going to first have the very first CBER product that's going to have an abbreviated presentation with justification. Then we'll have two justified presentations for drugs; and then we'll do two of the one slide abbreviated presentations. So first on the list, we have the CBER product Hizentra. Hizentra is a 20 percent liquid solution of human immune globulin, and it contains the amino acid proline. So, proline is really in the IGG agents as a stabilizer. Hizentra is indicated for the treatment of primary immunodeficiency; it's administered

subcutaneously. The pediatric use section of the label was changed in February 2011, to reflect the safety and effectiveness of Hizentra in individuals two-to-16 years of age, and that was based on a post-market study.

So just to review and sort of follow up on what Dr. Buch said for the justification for this product, really, there were no pediatric deaths in this review period. There were 22 serious adverse events in the U.S. that were consistent with the safety profile that's known on this, no new safety concerns, use is low in the pediatric population, and the labeling appears appropriate. So that's what's behind our choosing this. The full review is done, but when we gathered together, we felt this could go abbreviated. So if you look at the adverse event review that was for, like, this year here, it revealed 22 serious adverse events in children under 16 years of age. Most were infusion site reactions and others included respiratory tract infections, headache, pain, and vomiting. So some of those are constitutional symptoms that you see with the underlying condition, and these adverse events were seen in -- similar to what was in the clinical trials. So FDA plans to continue its standard ongoing safety monitoring for this, and we ask, does the committee concur with this?

CHAIRMAN TOWBIN: Thank you, Dr. Cope. I'd like to point out that Dr. Dracker and Dr. Reed have rejoined us at the

table. Oh, Dr. Reed is recused, pardon me. All right, so do people have questions, or concerns, or comments? Yes?

DR. WAGENER: This is Dr. Wagener. I just had a question on how you define "use is low." Is this relative to the adult use of the drug, or is it relative to the use of comparable medications in pediatrics, or is it an absolute number that we're using?

DR. COPE: I'll ask the division. Dr. Martin, you want to answer?

DR. MARTIN: We're not authorized to disclose any distribution data publically about this by the sponsor. In terms of the general question --

DR. WAGENER: I'm just asking the general --

DR. MARTIN: Right, right, right...

DR. WAGENER: The definition of "use is low," because this comes up in some of the other products later on, where relative to other product -- it may be something that's rarely used in children, but that's because it's rarely used; or it may be something that is used a lot in adults and rarely used in children.

DR. MARTIN: I actually -- I'd actually have to see from the prior presentation, if that sort of qualitative assessment of use actually figures into whether something's an abbreviated presentation or not. I mean, practically speaking,

on a day to day basis, it doesn't change anything that we're doing. So I'm not exactly sure why that line ended up on the slide, to be honest with you. I don't think -- is that -- can we -- Dr. Buch, is that one of the criteria that we were expected to look at in advance? I don't believe it was.

DR. BUCH: Yeah. I guess when we --

CHAIRMAN TOWBIN: Dr. Buch, if you could come to the microphone, we'll be able to capture your comments.

DR. MARTIN: Right, I guess what I'm trying to say I think there was an attempt to make qualitative summary statements that have to do with these criteria that we were expected to follow, to determine what to bring to the committee. But as I was saying, practically speaking, it doesn't influence our surveillance or what we report to you at all. We put just as much effort into it, whether there is high or low distribution.

DR. MURPHY: Barbara, could I just also ask you to --

CHAIRMAN TOWBIN: Dr. Murphy?

DR. MURPHY: Thank you. Remind the committee that, unlike the reviews that you're used to getting for drugs where we have those systems where we look at use outside of vaccines, where you know what the use is, there's a different -- there's a different system. So, I'm going to ask Dr. Buch to address that, too. So, we -- and I think the committee's seen there

have been times where we actually haven't been able to get some of the use data, have had to go back to the sponsor for some of the biologic products, and ask them to tell us what the use was. So I think what you're hearing is that that's a general goal that we want to make sure that this product doesn't have a lot of use, but certainly we're in the field of biologics we're having -- struggling with that metric, if you will.

DR. BUCH: I just wanted to point that the --

CHAIRMAN TOWBIN: Dr. Buch.

DR. BUCH: This is Dr. Buch, sorry. The indication is rare and even rarer in pediatrics. So that falls under the paradigm of, you know, low. And what I'd like you to focus on here is that there are no pediatric deaths in a review period, and no new safety concerns, which brings it to the abbreviated, according to the criteria that we just talked about. So --

DR. MARTIN: Right, so distribution is not one of the criteria, right?

DR. BUCH: No, distribution is not one of the criteria, except in the final category of full abbreviated, where there's little use at all. I mean, it's not even used; it's -- it's not even marketed. So that's not the case here. The case here is that the indication is such that in pediatrics the use would be completely low, just so rare that, I mean, the low is probably -- again, we're battling semantics here --

DR. MARTIN: Maybe a way to think about this is even if the use were high, qualitatively extremely high for this product --

DR. BUCH: The first three bullets.

DR. MARTIN: -- it would still have fallen into the same category of not having a live presentation under the criteria that have been worked out between the PAC and the Office of Pediatric Therapeutics.

DR. BUCH: Right, so the focus should be on the first three bullets here for this --

DR. MARTIN: However, there is one public piece of information in here that there was a survey by the Immune Deficiency Foundation and 26 percent of individuals with PID are children under 18. So there's one sort of qualitative piece that we are allowed to share.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: Bob Dracker. I just want to comment. The importance of a nonparental form of IVIGG is significant, especially for access to receive immunoglobulin therapy for children with immune deficiencies, and so the importance of the product is significant. The issue with IVIGG in general, and we see this even with the 10 percent solutions given parenterally is that the asthmatic effect can be very irritating. Now, when you start children on this product, even though it seems

convenient, it's prolonged subcutaneous infusion, and it's almost always irritating. If you look at the instance of local reactions, it's significant. And so you find that children may try the product and, as most of us here know, if the child doesn't want to get something, whether it's by mouth or by injection, you're not going to get it into them. And so, some of them may try it, but the actual market penetrance is relatively small. The other problem is that there's never really been a good head-to-head study and are looking at long term clinical advocacy of relatively low dose, chronic therapy versus episodic, monthly IVIGG therapy to show one is more effective or less effective than the other. Thank you.

CHAIRMAN TOWBIN: Thank you, Dr. Dracker. Dr. Martin.

DR. MARTIN: I just want to follow up the prior discussion with just some additional facts about distribution information that's probably worth the PAC reviewing. So just like drugs, we can always contact the sponsor, in this case, you know -- in the case of CBER products, individuals hold a license and distribute a product. And we can ask for the distribution data. That is commercial confidential information, so unless they explicitly give FDA permission, we are not allowed to disclose that in a public forum; however, U.S. special government employees may view that information in the PAC review memo itself. It just can't be discussed here in a public forum.

The other piece of this is that for biologics, we have access to the same -- by working with the Center for Drugs, we have access to the same drug distribution information that CDER does. It's just that often our products are not well captured in those systems, because those systems often focus on outpatient use. So there's actually some drugs which are used -- obviously many drugs which are used in patients, which are also not well captured in those systems, but, likewise, you'll see that, for instance, for IGs or also, there are also vaccines where often we need to look at other sources of data, because for various -- for other reasons, kind of at the other end of the spectrum, they're not necessarily given in a traditional outpatient setting, but may be given at a pharmacy, or may be given by a health department. So basically we use a combination of asking -- first of all under the regs, sponsors provide certain reports to us, but when we need to get date ranges that are necessary for the PAC, we'll send a special request and a request to disclose publically. But if that's denied, you'll still see it in the memo, and then from -- the second place is consulting with the Center for Drugs, for their information. And then also there's just our knowledge of the routine reporting that we receive from sponsors, or anything in the published literature. So I just wanted to let you know that that's -- it's not all that different between the centers, but we do our very best to

get a handle on distribution data. But again, that's why we're always talking about how surveillance is surveillance. You're trying to figure out what's going on from a lot of disparate pieces of data, both numerator and denominator, and that's why we have the many sentinel systems to amplify safety signals when we're trying to look at all this noisy data on the front end. Thanks. So, go.

DR. MURPHY: Okay, I think one of the -- Dianne Murphy here. One of the issues is that the committee has always said -- particularly because of the low use, they want to know what the denominator is, okay? They want to -- because they can't get any other good denominator out of airs or VAERS, or whatever it's called. So I think the question is one that we've always tried to give the committee use data, okay. So I think that's where they're coming from on this, is where, you know, we try to give them use data and we made the statement that the use is low. But I think what you're hearing is -- what was said is that we will give you what we can get, and if you need more data that is not public, we could always go back and ask for it, is, I think, is what you said --

DR. MARTIN: I'm actually saying it's in the memo right now.

DR. MURPHY: Well, there's no numbers here. If you look, it says -- it says "represent approximately the --" you

know, print four and B, print four and B, print four, and so it doesn't give them a number and what they got.

DR. MARTIN: If you look in Section 4 of the memo, you'll find the distribution data.

DR. MURPHY: Yeah, that's what I'm saying, if you look at that here.

DR. MARTIN: Where are you, Dianne? Are you on Page 3?

DR. MURPHY: Yeah, [affirmative].

DR. MARTIN: All right, just look on Page 3 and Page 4, you'll find it.

CHAIRMAN TOWBIN: Here comes Dr. Buch.

DR. BUCH: I just, in the interest of disclosure, would say the nonredacted memo is public. The redacted memo is for PAC member review only, and not discussion at this meeting, please.

CHAIRMAN TOWBIN: And therein I think is the source of the difference.

DR. MURPHY: Yeah, yeah. So we often -- as you guys have complained about getting the redacted and say you can't make any sense out of it. If there's not a lot of redaction, we go ahead and send it to you. In this case there wasn't a lot of redaction. It just happened to be in that area. So, I -- because -- yeah, I think that's what the problem is, is you're

looking at the copy that has the B -- the [unintelligible] B and 4, instead of the actual numbers, but the unredacted we can send you, and we can give you, you know, but not publically.

CHAIRMAN TOWBIN: Dr. Wagener.

DR. WAGENER: I think this has gone down a different road and a different highway than I originally had planned. I actually know what the numbers are, because I did read the nonredacted. My point was that in the information we've been given about the whole process, the issue of low use comes up multiple times, but there's a never a definition for what is low use, and I would just give you the example. In Hizentra, let's say that there are only 100 children in the United States that would be appropriate for this to be used in, and we see an SAE rate of 23. While that's low use, it's high frequency. I would assume people would accept that, and so I was simply asking, in defining all of these products where we put use as one of the criteria for the presentation -- I trust the FDA is looking at it, but where we put that as our criteria, I just wondered what the definition of low use is, and I could see it defined in many ways. I could see it relative to the adult use; I could see it relative to the frequency of disease for which this therapy is used; or I could see it as an absolute number. Somebody might come out and say "If they're less than 10,000 doses given in children, we're going to call it low use." But I think if we're

going to have that in our definition of what the presentations will -- what will determine the type of presentation, then it should be clear what that definition is.

DR. BUCH: Can I just quickly address this?

CHAIRMAN TOWBIN: Dr. Buch is returning to the microphone.

DR. BUCH: And I'll be brief. So, folks who have the presentation that I gave, look on slide number 15 or 16. The term "use" is only used "little or no use," meaning it's not distributed. "Low use" here has nothing to do with the fact that it's a justified abbreviated presentation. Justified presentation has these criteria. So we're focusing on something that's really unimportant. We should move on.

DR. MURPHY: Well, I think Dr. Wagener is just saying if we're going to put it up there, then we need to be able to explain it. So I totally agree with you and I think that we'll revisit this, because I think one of the problems here is that it started with a completely abbreviated. That was the criteria, no deaths, fewer serious, and either not marketed or almost no use, and we didn't define it, okay. Then as we got into justified abbreviated, we, you know, sort of wanted to indicate that as a product had a lot of use in children, such as vaccines, or antibiotics that, you know, we would expect that we're going to have some reportable events. But we still might

think that it was proper to do a justified. And that's why it's called justified; we're going to explain to you why it's justified. So I think we'll have to revisit whether we use that term in the justified abbreviated, because it sounds like we -- or come up with a better definition.

CHAIRMAN TOWBIN: Right, I think that perhaps what Dr. Wagener is saying here, although he will correct me if I say it wrong, is that if low use is one of the reasons for a justified abbreviated review, that will be spelled out what you mean under those circumstances, and not be assumed. All right, so we're ready to return to the slide. And what we're being asked is whether the committee concurs with returning Hizentra to standard ongoing safety monitoring. And Dr. Mink, could we begin with you?

DR. MINK: I concur.

CHAIRMAN TOWBIN: Dr. Reed is recused.

DR. SANTANA: Dr. Santana concurs.

DR. MCGOUGH: Dr. McGough concurs.

DR. ROSENTHAL: Geoff Rosenthal, concur.

DR. WHITE: Michael White, concur.

DR. BAKER: Susan Baker, concur.

DR. HUDAK: Mark Hudak agrees.

DR. CATALETTO: Mary Cataletto, concur.

DR. LARUSSA: Phil LaRussa, concur.

DR. DRACKER: Bob Dracker, concur.

DR. FRANCO: Israel Franco, concur.

DR. GLASIER: Charles Glasier, concur.

DR. WAGENER: Jeff Wagener, I agree.

DR. WIEFLING: Bridgette Wiefling, I agree.

MS. CELENTO: Amy Celento, concur.

CHAIRMAN TOWBIN: Thank you very much. So, I think
now, Dr. Cope, we're going to talk about Alimta.

CDER JUSTIFIED ABBREVIATED: RATIONALE PROVIDED --

ALIMTA (PEMETREXED DISODIUM)

DR. COPE: Okay, we're going to move on to Alimta. Okay, so we were switching now to drug products. So I'm just -- for starters because we're switching now to drugs, I'm just putting the justified abbreviated presentation criteria that we've standardly done in the past, and yes, we need to define, I guess --

CHAIRMAN TOWBIN: Dr. Cope, can I interrupt you for one moment? I think we missed Dr. Cnaan, and that was my error. Dr. Cnaan, please forgive me.

DR. CNAAN: I concur.

CHAIRMAN TOWBIN: Thank you. Now, Dr. Cope, pardon my interrupting you.

DR. COPE: That's all right. So I just got before you the standard criteria that we've been using for the drugs for the abbreviated reviews. When we basically have most of the following criteria are met, then we will go with justified abbreviated presentation. Again, a few slides with giving you rationale why we think it can go abbreviated. So again, its use; not marketed; no deaths or deaths because of underlying disease, not because of the drug at hand; few, if any, serious adverse events or the events may be compatible with the

underlying disease; no safety signals were identified in the full review; and the product labeling seems appropriate. Okay, so I'm just going to move to Alimta. So Alimta is a folate analog metabolic inhibitor indicated for locally advanced or metastatic non-small cell lung cancer and for malignant pleural mesothelioma in adults. So I might just mention it was studied in refractory and solid tumors like osteosarcoma, rhabdomyosarcoma, and neuroblastoma in Ewing's, but efficacy was not shown. So, really, there were no deaths, four serious adverse events, no safety signal, use is low. It really isn't being used a lot; it just didn't work. And the product labeling seems appropriate. Please note that this review covers an eight-year period, and again, there were only four events. There was -- just to go through them, there was a three-year-old with a brain stem ependymoma who got perianal ulceration a few days later, and skin rash, and disclimation are in the label. There was a nine-year-old with an anaplastic oligodendroglioma, and experienced tumor hemorrhage and worsening of hydrocephalus. This was not felt to be related to the drug. Then there was a six-year-old with a medulloblastoma who had a syncopal episode 15 days after, and so the time to event period really made this unlikely an association. And then there a literature report of an eleven-year-old with recurrent peritoneal mesothelioma, who

had neutropenia, thrombocytopenia, and pyrexia. And all of those are labeled events. And just to look at the use, there was less than 1 percent of patients with a prescription or medical claim for the zero-to-16-year-olds during that time period. So FDA plans to continue its standard ongoing routine monitoring. Does the committee concur?

CHAIRMAN TOWBIN: All right, we're open for comments or questions. I don't see any, and so I think I should do it right this time, beginning with Dr. Cnaan.

DR. CNAAN: I agree with the recommendation.

DR. MINK: John Mink. I agree.

DR. REED: Michael Reed. I agree.

DR. SANTANA: Victor Santana. I concur with the recommendation.

DR. MCGOUGH: Dr. McGough agrees.

DR. ROSENTHAL: Geoff Rosenthal. I agree.

DR. WHITE: Michael White. I concur.

DR. BAKER: Susan Baker, concur.

DR. HUDAK: Mark Hudak, agree.

DR. CATALETTO: Mary Cataletto, concur.

DR. LARUSSA: Philip LaRussa, concur.

DR. DRACKER: Bobby Dracker, concur.

DR. FRANCO: Israel Franco, concur.

DR. GLASIER: Charles Glasier, concur.

DR. WAGENER: Jeff Wagener. I agree.

DR. WIEFLING: Bridgette Wiefling. I concur.

MS. CELENTO: Amy Celento. I concur.

CHAIRMAN TOWBIN: Thank you very much. So on to the next -- Dr. Cope. I think we're going to talk about Gadavist.

GADAVIST (GADOBUTROL)

DR. COPE: So we're moving to the contrast agent and I might say to -- just to acknowledge that there are people from imaging -- all the divisions that are associated with these drug and CBER products are sitting at the table if you should have questions too.

DR. KREFTING: Allow me to introduce myself. Ira Krefting, deputy director for Safety Division of Medical Imaging Products.

CHAIRMAN TOWBIN: Thank you and welcome.

DR. COPE: So again, for the Gadavist, like the others, you've gotten the full package of review materials. This is an intravenous used in diagnostic MRIs as a contrast agent for adults and children 2 years and older to detect and visualize the areas with disrupted blood brain barrier and abnormal vascularity of the CNS. Justification was this: there were no deaths, few SAEs, no safety signal, and the product labeling was appropriate, as we reviewed it all. And during this time period, there were no deaths in six AEs. Note that five out of the six were foreign reports and there were basically two cases of hypersensitivity reaction; one case of respiratory insufficiency; one that had insufficient data about an anaphylactic type reaction or pulmonary edema; and then there was a miscellaneous symptom case and an overdose. And the

overdose was sent to the Division of Medication Error and Prevention Analysis to look into that to see if there was any safety signal over there. The drug use basically for the approval age for 2 to 16 years of age was about 4 percent of the hospital billing for Gadavist. So we'll return and say that FDA will continue its standard ongoing safety monitoring and does the committee concur?

CHAIRMAN TOWBIN: All right, questions? Dr. Wagener?

DR. WAGENER: Jeff Wagener. Actually I've a combination of questions but I don't know if we have the answers, and that would be do you know the hypersensitivity reactions? Were those on first exposure or were those on subsequent exposure? I believe when we looked at this drug, or a similar one a couple of years ago, we found scenarios where people had received many, many doses of the drug before hypersensitivity was experienced. So I was wondering in this case, first exposure hypersensitivity or is it a subsequent exposure?

DR. COPE: I'm not so sure. I do recall that that must have been the multi-hands [spelled phonetically] --

DR. WAGENER: [affirmative]

DR. COPE: -- and that particular one had an association with nephrogenic systemic fibrosis. But you're

asking a completely different question. I'm not sure which you know --

DR. HAUSMAN: Dr. Carolyn Volpe is up at the table with us. She was the primary reviewer.

DR. COPE: Oh, okay.

DR. KREFTING: You wish to give some information first, or...?

DR. VOLPE: Sure, I can --

DR. KREFTING: Okay, I'll speak also, but go ahead.

DR. VOLPE: Okay.

DR. KREFTING: Ladies first.

DR. VOLPE: [laughs] We don't actually have that information, but they did not mention that this was a subsequent exposure. So I don't know if they had this medication before.

DR. HAUSMAN: We don't have the information. The reports didn't include it.

DR. KREFTING: Yes, Ira Krefting. I think we're talking about little children here. Conceivably it was the first exposure. I think what you're referring to in terms of multiple exposures was our concern about the development of nephrogenic systemic fibrosis, NSF. As you know, our product labeling across the class for these gadolinium agents has a concern about repetitive dosing, and indeed when you look at the case reports, especially from earlier in the past decade, and

for that matter in the last century, people who seem to have developed this problem were those who received multiple upon multiple gadolinium imaging studies.

So granted at least we think the theory of hypersensitivity reaction is not immunogenic. By that I mean it's not necessarily an immunologic cascade that fires off through mass-cell degranulation, et cetera. The -- it's of some other mechanism. So that, if we continue -- if we believe in that theory -- so that can happen on the first exposure, and we could call that anaphylactoid because it's the first exposure, but it can also happen subsequently. I don't have the literature references for you, but there seems to be that belief that it can happen -- that people can have an allergic reaction first time, they're going to have the second time, et cetera.

CHAIRMAN TOWBIN: Dr. Franco?

DR. FRANCO: I -- you know, I wonder whether the fact that the -- whether the bottle or the cap is latex and since these children have numerous latex exposures, how many of these reactions were really latex allergies? And that's something that should be probably looked at. You know, it may not even be due to the drug.

DR. KREFTING: Sorry, could you just clarify -- when you say latex, in terms of delivery system or in terms of the --

DR. FRANCO: Anything in the delivery system associated with latex. And since these many patients have had numerous surgeries in the nervous system, and we know there's a direct relationship with latex allergies in children who have had numerous spinal surgeries or central nervous system surgeries, that's the mechanism why we see such a high instance of latex allergies in spina bifida cases. How many of these -- how many of these could have been due -- simply due to latex allergy with latex being introduced somewhere along the system when they were being given the medication?

DR. KREFTING: Certainly the introduction of Lasix anywhere in the treatment course of these --

DR. FRANCO: Not Lasix; latex.

DR. KREFTING: Latex, yeah -- is problematic and some of these are foreign cases so that would be an area of exploration in terms of -- as I understand it, we've looked at -- from the IV infusion systems, at least those in the United States, we have not found leeching of any of the plastic products as they flow into the patient.

CHAIRMAN TOWBIN: Yes, Dr. LaRussa.

DR. LARUSSA: So just a point of clarification -- when you use a term like hypersensitivity-type reaction, is -- are you using that in terms of that's what was used in the chart or after review of the symptoms you decided that the symptoms were

consistent with a hypersensitivity reaction? And that's generic for any diagnosis.

DR. HAUSMAN: This is Ethan Hausman. I'll respond for the division for that. It can be a combination. When we get the reports that come in through the MedWatch reports, they can be as specific or as general as the reporting person makes them. Sometimes they come in with phrases like hypersensitivity reaction. Sometimes they'll come in with laryngeal edema, hives, pruritus, things of that nature. The way the reviews are performed, we try to use the terms that are most consistent with what the reports says. If the report gives a constellation of systems that's consistent with anaphylaxis according to recently published guidelines, that may be a scenario where we would say it's anaphylaxis even though the report doesn't state it as such, but it fully describes it to the point where anybody who's generally educated in the field could make that call. So it's a combination.

CHAIRMAN TOWBIN: Other comments or questions? Dr. Cnaan.

DR. CNAAN: To the issue of use that was raised before. For this particular case it seems to translate to about 2,000 kids per the reported period approximately. And the other interesting thing is that the number of reports -- the percentage of reports, of pediatric reports of events were 3

percent of the total number of events and were given by the slide that the percentage of use is 4 percent. So in general it seems like, at least in this one, the kids and the adults' safety profile seems similar for whatever that's worth.

CHAIRMAN TOWBIN: Dr. Franco.

DR. FRANCO: Yeah, just go back to the issue of latex and it could just be a pair of gloves in the room, okay, or gloves or anything else in the room that was there, and then some of these children are so severely allergic that that would trigger a reaction. So I think it's a very important confounding factor in these cases.

DR. KREFTING: Yes, sir. To respond to you, I think that's a very good point. The -- and to illustrate that further, the -- some of the cases that I think have been presented -- remember, these are little kids. They sometimes need to be sedated to the extent of some form of general anesthesia, and the other confounding factors are allergy or allergic reactions or other cardiovascular reactions to the variety of anesthetic agents that are provided to these kids. So there are multiple confounders, and as you heard from Dr. Hausman, trying to sort it out at times from the raw reports that come to us is a challenging process.

CHAIRMAN TOWBIN: So perhaps we're ready now to move on to a vote. So the committee is being asked whether it

concur. Dr. -- I'm sorry, Ms. Celento, if we could start with you?

MS. CELENTO: Amy Celento. I concur.

DR. WIEFLING: Bridgette Wiefeling. I concur.

DR. WAGENER: Jeff Wagener. I agree.

DR. GLASIER: Charles Glasier. I concur.

DR. FRANCO: Israel Franco. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. LARUSSA: Phil LaRussa. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. HUDAK: Mark Hudak. I agree.

DR. BAKER: Susan Baker. I concur.

DR. WHITE: Michael White. I concur.

DR. ROSENTHAL: Geoff Rosenthal, agree.

DR. MCGOUGH: James McGough, agree.

DR. SANTANA: Victor Santana. I concur.

DR. REED: Michael Reed. I concur.

DR. MINK: John Mink. I concur.

DR. CNAAN: Avital Cnaan. I concur.

CHAIRMAN TOWBIN: All right. Thank you very much. So now let's talk about Kedbumin.

ABBREVIATED: CBER AND CDER -- KEDBUMIN ALBUMIN (HUMAN),
NATROBA (SPINOSAD)

DR. COPE: Okay. All right, so now we're moving to two products that, basically, again, most but not all of the criteria were met and we -- after full review, we felt these could go with a single slide presentation. Again, the criteria: little, if any, use; not marketed; few, if any, serious adverse events; no deaths; no safety signal was identified after a full review; and the product labeling seemed appropriate.

And you have the full background. And basically, both products are put on this slide. So the Kedbumin is an Albumin 25 percent solution, and the Natroba is a topical head lice treatment. And we plan to continue the standard ongoing safety monitoring for these products. Does the committee concur? And we just ask that you take them one by one and vote. But discussion, first thing.

CHAIRMAN TOWBIN: All right, so are there comments or questions? Ms. Celento.

MS. CELENTO: Amy Celento. Just back to the topic of low use, little use, Kedbumin here has "*more than a little use," so, you know, I just think that going forward, it -- we might need some more clarity around little, low, more than a little, what does that mean?

DR. COPE: Right. Well, we put the both of those have more than a little use, so those were -- that's why it didn't fit full criteria, I guess. So..

CHAIRMAN TOWBIN: All right. Anyone else? Though these are abbreviated reviews, we still have our questions. Dr. Wagener.

DR. WAGENER: I would just hope that nobody gets these confused and puts the Albumin on the head and --

[laughter]

DR. WAGENER: -- whatever.

CHAIRMAN TOWBIN: Thank you very much for that pointed remark [laughs]. So if we could begin with Dr. Cnaan.

DR. CNAAN: Regarding the first one, the Albumin, I concur.

DR. MINK: John Mink. I concur.

DR. REED: Michael Reed. I concur.

DR. SANTANA: Victor Santana for Ked-Albumin. I concur.

DR. MCGOUGH: James McGough. I concur.

DR. ROSENTHAL: Geoff Rosenthal. I agree as well.

DR. WHITE: Michael White. I concur.

DR. BAKER: Susan Baker for Ked-Albumin. I concur.

DR. HUDAK: Mark Hudak. I agree for Kedbumin.

DR. CATALETTO: Mary Cataletto. I agree for Kedbumin.

DR. LARUSSA: Phil LaRussa. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. FRANCO: Israel Franco. I concur.

DR. GLASIER: Charles Glasier. I concur.

DR. WAGENER: Jeff Wagener. I agree.

DR. WIEFLING: Bridgette Wiefling. I agree.

MS. CELENTO: Amy Celento. I concur.

CHAIRMAN TOWBIN: Oh, very well. So after that heady vote, we can move on to Natroba. Is there any discussion about Natroba that we wish to have or ask about? Then I think we're ready to begin. Ms. Celento.

MS. CELENTO: Amy Celento. I concur.

DR. WIEFLING: Bridgette Wiefling. I concur.

DR. WAGENER: Jeff Wagener. I agree.

DR. GLASIER: Charles Glasier. I concur.

DR. FRANCO: Israel Franco. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. LARUSSA: Phil LaRussa. I concur.

DR. CATALETTO: Mary Cataletto. I concur.

DR. HUDAK: Mark Hudak. I agree.

DR. BAKER: Susan Baker. I concur.

DR. WHITE: Michael White. I concur.

DR. ROSENTHAL: Geoff Rosenthal. I agree as well.

DR. MCGOUGH: James McGough. I agree.

DR. SANTANA: Victor Santana. I concur for Natroba.

DR. REED: Michael Reed. I concur.

DR. MINK: John Mink. I concur.

DR. CNAAN: Avital Cnaan. I concur.

CHAIRMAN TOWBIN: Thank you very much. So Dr. Cope, I think we're now going to talk about our designated abbreviated review process of three products.

DESIGNATED ABBREVIATED REVIEW PROCESS --

UROXATRAL (ALFUZOSIN HYDROCHLORIDE), CREON (PANCRELIPASE),
ZENPEP (PANCRELIPASE)

DR. COPE: Right. So basically they're the three products that are -- that were -- went through this designated abbreviated review process. So I thought I'd take just a couple of slides to go over and remind you what this process is that we started about a year ago that FDA had proposed and the committee had agreed. Basically in the process the FDA does the full review, as with all the others, and determines that the product meets all the criteria to go abbreviated. And one member is selected from the PAC who goes through the conflict of interest process and then that member will be the only one to receive the full package and do an in-depth review and all the rest of the SGEs and PAC members can review everything that -- when it's posted on the web.

And at the meeting, then it's known that the members either voted or not to go along with the process for that particular product. There's no presentation and at the meeting today, the designated member will make recommendations to FDA and do the voting by he or she. If yes, the product will return to routine monitoring the standard question that's asked. If

no, the product then has to come back for a full standard review. Other PAC members will listen, so when the designated reviewer speaks, you all can listen, but there is no discussion and no voter participation at all during that time. And this is just a little flow sheet that goes through that that we've -- we go through the criteria, we identify the reviewer who gets everything, he does the in-depth review, and then votes. And then as you see down here, too, that ,again, the committee members can vote for the process -- they vote for the process, but if they were to reject the routine monitoring, then it has to go back for a standard review, and actually that's happening later today with Moxeza. So -- but I just wanted to remind people and publicly state what this is. So with that...

CHAIRMAN TOWBIN: Very well. So for today's meeting, three products meet the criteria for designated reviewer process. Two of the permanent PAC members were assigned to review three of the abbreviated products. These products are Uroxatral, where Dr. Mink is the reviewer; Creon, where Dr. Hudak is the reviewer; Zenpep, where Dr. Hudak is once again helping us. Please remember that each of these designated reviewers has been analyzed for potential conflict of interests that they may have with their assigned products. As you've seen, when anyone on the panel has a conflict of interest, either through a direct interest or attributed to, in some

cases, quite remote interests, we ask those people to step away from the table and not to participate in the discussion. Only those who've been cleared through the conflict of interest process can participate as advisors to the FDA on this committee. Therefore, at this point, we will let the designated reviewers provide advice to the FDA. For the rest of us at the table, including me, who have been through the conflict of entrance -- interest clearance process for these products, we should not be providing advice to the FDA on these products at this time. So Dr. Mink.

DR. MINK: With regard to Uroxatral, I concur with the -- and in favor return to routine monitoring.

CHAIRMAN TOWBIN: Very well. Dr. Hudak?

DR. HUDAK: Didn't quite know what to expect, but certainly with respect to Creon and Zenpep, which are the pancreatic enzyme products, I also concur with return to standard monitoring for both.

CHAIRMAN TOWBIN: Very well. Just to remind you all that you can -- and to others who may be in this process in the future -- it is acceptable to offer remarks or some summary of your review. So you are advising the FDA. It's fine that you've said what you've said, but I don't want you to think that your comments need to be completely truncated to just answering the question. Thank you.

DR. MURPHY: Yes, we -- again, this isn't a process where the -- you all are in a, what, four, now [laughs], for trying this and we appreciate the participation by the committee in this and the fact that you're willing to assign somebody on the committee to do this for you for certain products. So we've had a variety of comments to very brief ones. So -- but it -- the only people who can't talk about it -- everybody else on the committee who hasn't gone through conflict of interest, but you all are welcome to make any comments you wish.

CHAIRMAN TOWBIN: And if at some point people do have some feedback for the FDA about this process, that also is something that is welcome. So either, you know -- at some point, if people have any thoughts or views about this, it's okay to state them as we are to advise the FDA on this process. Dr. Hudak, did you have a comment?

DR. HUDAK: Well, since comments were solicited, I'll just make one on this. These two products, pancreatic enzyme products had extensive information provided about adverse events and as in pediatrics, most of the use of these products is for patients of cystic fibrosis it's very interesting that the adverse events -- the serious adverse events that were reported were basically confined to incidents of distal ileal obstruction syndrome and also pseudomonas exacerbations. For the distal ileal obstruction syndrome, reports it was consistent with

what's in the literature. For the pseudomonas exacerbations, it was well below what we see in clinical practice. So it just pointed out the idiosyncrasy perhaps of what gets reported as an adverse event.

CHAIRMAN TOWBIN: Thank you for that. So I think we've earned ourselves a bit of a break and we will reconvene, I understand, at 10:00.

STANDARD REVIEW OF ADVERSE EVENT PRESENTATIONS --

MOXEZA (MOXIFLOXACIN OPHTHALMIC SOLUTION 0.5%)

All right, I think we're ready to reconvene, so if we can have everybody come, and sit down, and get ready. All right, so we're going to begin with a discussion of Moxeza, and you may recall that Dr. Cope said that we were going to review this product fully. It was slated at the last meeting for an abbreviated review, but as per the guidelines, one of the committee members had some concerns about that process for it, and so it comes back to us. Dr. Taylor is going to tell us about it for a full review, and just to say Dr. Taylor has served as a medical officer with pediatric and maternal health staff for five years. Prior to joining the FDA, Dr. Taylor was the deputy director, and then acting director of the Division of Clinical Quality in the Health Resources and Services Administration, implementing the quality improvement strategy for community health centers. Dr. Taylor served as a pediatrician in the United States Army for nine years and as an urgent care pediatrician with Egleston Children's Healthcare System in Atlanta, Georgia for two years. She received her medical degree from Howard University College of Medicine and completed a residency in pediatrics at Madigan Army Medical Center in Tacoma, Washington. She received a Master of Health Science and

Health Policy at Johns Hopkins University, the Bloomberg School of Public Health. Welcome, Dr. Taylor.

DR. TAYLOR: Thank you. I will be presenting the pediatric focus safety review for Moxeza, moxifloxacin hydrochloride ophthalmic solution 0.5 percent. And before I continue, I just want to bring your attention to a typo in the titles of the slides, that it has 5 percent. It should be 0.5 percent. So, this is an ophthalmic solution, 0.5 percent. It's a topical fluoroquinolone, anti-infective. The manufacturer is Alcon Pharmaceuticals Ltd. and original market approval was November 19th, 2010. The indication is treatment of bacterial conjunctivitis caused by susceptible strains. I'm going to go through the pediatric studies that were done and a little bit of information that's from the labeling. A randomized vehicle controlled study of adults and pediatric patients greater than one month of age was conducted. Moxeza was superior to its vehicle for both clinical and microbiological outcomes, and the labeling states that safety and effectiveness of Moxeza solution in infants below four months of age have not been established, and also states that there's no evidence that the ophthalmic administration of Moxifloxacin has any effect on weight bearing joints even though oral administration of some quinolones has been shown to cause atrophy in immature animals.

This is some information about the drug utilization.

You'll see in the first two columns of pediatric population numbers zero-to-1 year, 41,000 prescriptions and 39,000 unique patients, which is 18 percent of the total population. In the 2-to-16 year range, there are 109,000 prescriptions and 105,000 unique patients, and this of course is over a period from November, 2010 to March, 2012. The column in red is the adult information. The top diagnosis code is conjunctivitis. The top prescribing specialty is primarily pediatrics, but then also general practice family medicine, doctor of osteopathy. So, this chart shows you the number of adverse event reports. You'll see that there was one serious adverse event report, in pediatric population, and I'll just point you to the five unknown age reports -- serious reports as well. There were -- none of the five reports in the age unknown reporting. Serious outcomes involve pediatric patients, so we continue with a case of one. And as of December 17th, 2012, no new cases were reported since the last safety review on June 6, 2012. So if you remember when we first presented it as a DAR product, and then, in preparation for this committee meeting, we went back to look to see if any other patient reports had come up, and none had.

Just to go over the one serious, non-fatal adverse event. It's a consumer who reported her 10-year-old son developed breathing problems described as wheezing on March 26,

2011, after starting Moxeza for pink eye. No medical history was provided other than that her son was allergic to cephalosporins. She took her son to the hospital. The son was provided breathing treatments at the hospital without effect. Moxeza was discontinued that same day and they reported that resolved four days later. So this concludes a pediatric focus safety review. There were no new safety signals identified and we recommend continued routine monitoring. And our question is does the committee concur? And I just want to say thank you to the following people for their help with this presentation.

APPROACH TO PEDIATRIC BACTERIAL CONJUNCTIVITIS

CHAIRMAN TOWBIN: Thank, you Dr. Taylor. I believe we're going to have a presentation by Dr. Chambers before we vote on the committee questions. So, Dr. Chambers. Dr. Chambers is the deputy director of the Division of Transplant and Ophthalmology Products in the Center for Drug Evaluation and Research at the FDA. He received an undergraduate degree from Colgate University and completed medical school training in ophthalmology at the George Washington University School of Medicine. He's clinical professor of ophthalmology and adjunct assistant professor of computer medicine at the George Washington University. He joined the FDA in 1987 as a primary reviewer for ophthalmic drug products, and in 1990 he became a supervisory medical officer for ophthalmologic drug products. In this capacity, Dr. Chambers has supervisory responsibility for the clinical review of ophthalmologic drug products and ophthalmic therapeutic biologic products submitted to the FDA for study and potential approval. Dr. Chambers is the recipient of numerous public health service FDA and Center for Drug Evaluation research awards for his work with the FDA, and he serves as the American Academy of Ophthalmology's Delegate to the United States Pharmacopeial Convention.

DR. CHAMBERS: Thank you very much. I think that my

bio was longer than my presentation is going to be, but I was asked to give you a brief idea of what we go through as far as approving products for bacterial conjunctivitis within pediatrics. So we actually have three separate indications that can potentially get related to bacterial conjunctivitis. So, the first is treatment of bacterial conjunctivitis, which we give to products that study patient's age one month and above. Then, we have a different term that's used for bacterial infections of the eye under one month, primarily because the source is likely to be something related to birth, and that's treatment of ophthalmia neonatorum. We also have a prevention of ophthalmia neonatorum required by law in most states, and that basically is designed to look at those products that are designed to prevent ophthalmia neonatorum, and are given within the first 12 hours after birth. So for bacterial conjunctivitis, we ask for two adequate and well-controlled trials. One of them must be a superiority trial. So you have to beat something, whether it's another anti-infective or a vehicle. Our vehicles are not completely innocuous. The vehicles, because they are multi-drop products, will have a preservative in them. So you're actually beating a product that does have some antimicrobial activity, and the expectation is not that you are necessarily curing bacterial conjunctivitis. Bacterial conjunctivitis, in most cases is a self-limited

disease, but you are speeding up the process. So we look at a shorter timeframe and look to see if you're making the disease go away faster. We asked people to do studies for bacterial conjunctivitis at one month of age or above, and most people will try to establish efficacy somewhere between day three and eight because that's the place where it's easiest to differentiate a faster cure.

The labeling then describes a faster resolution of the symptoms. We don't have culture capability to be able to detect every last bug that's within the eye. We want to make sure that you get completely rid of the bacteria, so we routinely label all of our products for seven days of treatment, recognizing we can't tell exactly when you've gotten rid of all the bugs. This has been historically done this way for years. We then look at clinical cures by age, including by month when we have younger kids, and we look to see where we have at least five kids clinically cured. And we take the lowest age where we -- the first point where we get five children who have done well, and we limit it for that age. So in the case of Moxe, you saw it's -- it's recommended for children four months and above, because we had, in this case, seven kids that were under that who did well. To give you an idea of what the different products that are approved for bacterial conjunctivitis are, a number of them are currently approved for one year and above, some at two

months, some at four months. While we encourage people to study lower ages, we're not always successful in getting people to study all ages, but when we can encourage it, we do.

For ophthalmia neonatorum, again, we're looking at both prevention and treatment. We're looking at things in the first month of life or within the first 12 hours of life. The only product that has really tried to get that indication has been Azithromycin. It is the common standard that's used throughout the country, and was -- and its approval was based on adequate and well-controlled trials approximately 28 years ago. And I'm happy to take questions.

CHAIRMAN TOWBIN: Yes, Dr. Santana.

DR. SANTANA: This is just a question for clarification. So when you were discussing Slide 3, you commented -- because I wrote it down, I was struck by the comment -- that you look at shorter time to resolution, not cure. But then when you presented the slide on labeling, you talk about cure. So I was kind of a little bit not clear of is cure in the labeling the resolution within that period of time?

DR. CHAMBERS: I'm sorry, yes. Cure as I used it was resolution of all signs and symptoms.

DR. SANTANA: It's not bacterial cure? Okay.

DR. MURPHY: Yeah, I think that's --

DR. CHAMBERS: Correct, and that's --

DR. MURPHY: This is Dianne. That's the difference is you can have a microbiologic resolution and a clinical resolution, correct?

DR. CHAMBERS: Yeah, well when we're looking at -- when we -- when I use the term cure, I'm talking about resolution of all signs and symptoms.

DR. SANTANA: Okay, and that's what you're addressing in the labeling slide, right?

DR. CHAMBERS: That's correct.

DR. SANTANA: That type of cure?

DR. CHAMBERS: Yep, and the percentages we list are based on that, too.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: Could you just clarify, on Slide 5, product label for the lowest age greater than the month in which five patients were cured on treatment? Is that regardless of the number of patients studied at that age?

DR. CHAMBERS: That's correct.

DR. LARUSSA: So if -- you know, to take the extreme, if one percent of the patients studied at that age were cured, you would still use that age as the okay for a product label?

DR. CHAMBERS: I'm sorry, say that one more time.

DR. LARUSSA: So let's say one out of 100 -- 5 out of 500 patients at one month of age were cured, you would have one

month of age as the -- in the product label as a acceptable use?

DR. CHAMBERS: We would not. As I say, we do look at every particular age along there, and look at the cure rates. If we saw a cure rate that was disproportionate to the overall product, we would raise questions about that particular age, and we probably would not follow the process that I'm talking about. These are all individual reviews, with not an automatic criteria that has a machine go and do it. We look all the way through. If we see an abnormality anywhere within the pediatric age group or even in the elderly that's disproportionate to what we're seeing for the rest of the product, we would contend to either exclude or label that concern, or further study it.

DR. LARUSSA: So, you might want to rephrase this in some way.

DR. CHAMBERS: Agree.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: Just two quick comments. First is that something that's very important for ophthalmologics, especially in children is tolerance, because of it burns or the kids do not like the application of it; it's a nightmare for the parents. And the one thing I've noticed personally, with Moxeza at least, is they tolerate it very well. It's been my own personal experience. But besides that, the other question I had is

almost a free consult question from you, and that is we constantly see children with conjunctivitis we use drops on, regardless of the type of drop. And as long as they're on a drop, even just one dose and they can go back to day care. So it's just a question for me of what's appropriate length of therapy before there's not a risk of infectivity to other children.

DR. CHAMBERS: Dealing with the first comment you made, we routinely ask for what we call comfort studies. So studies when you apply the drop, how does it feel going in? Because we want to avoid problems where people won't take the drops and get a partial course of therapy because it stings or burns too much. We can't do anything about our dilating drops; you have to put up with that. But everything else we look at for comfort. The second, if you base it on bacterial eradication of what we typically are able to culture, by 48 hours you won't culture organisms. Now, whether that's the best criteria to go back on or not, I don't know, but as far as being able to prove a culture within 48 hours of using a drop, you won't pick up bacteria.

DR. DRACKER: Can I give the mothers your name and email address, and say that they can't go back until they're on therapy for 48 yours?

CHAIRMAN TOWBIN: I don't think that he should answer

that question, Dr. Dracker. Dr. Wagener?

DR. WAGENER: So this is sort of a safety question. Repeat exposure historically has been a problem with eye drops, and does the FDA require any repeat exposure experience prior to approval? And if not, do I interpret that to mean that it's the post-approval safety or post-marketing commitments would be the only way we would determine safety for a repeat exposure?

DR. CHAMBERS: Repeat exposure you mean a second seven day course or you mean within the --

DR. WAGENER: A second exposure to the drug, either ophthalmologically or systemically, where they might experience an allergic reaction.

DR. CHAMBERS: We do not routinely require a repeat exposure to products prior to approval. The assumption, for better or worse, is that in the clinical trials that we run, we will pick up those types of events because we try and get as broad a population as possible. Clearly, if you are initially approved -- if you're initially reviewing a new molecular entity, you are not likely to get that in the original clinical trials, and we would only pick that up in post-marketing. That's correct.

DR. WAGENER: Do you routinely have a post-marketing commitment on companies that have ophthalmologic products like this

DR. CHAMBERS: We do not routinely require studies. We do routinely require that they monitor adverse advents and report those.

CHAIRMAN TOWBIN: So, perhaps we're ready to move along and vote on the question that Dr. Taylor posed to us about whether we concur with returning Moxeza to routine monitoring. Ms. Celento.

MS. CELENTO: Amy Celento. I concur.

DR. WIEFLING: Bridgette Wiefeling, I concur.

DR. WAGENER: Jeff Wagener, I concur.

DR. GLASIER: Charles Glasier, I concur.

DR. FRANCO: Israel Franco, I concur.

DR. DRACKER: Bob Dracker, I concur.

DR. LARUSSA: Phil LaRussa, I concur.

DR. CATALETTO: Mary Cataletto, I concur.

DR. HUDAK: Mark Hudak, I agree.

DR. BAKER: Susan Baker, I concur.

DR. WHITE: Michael White, I concur.

DR. ROSENTHAL: Geoff Rosenthal, I concur, but it's -- but I'm -- I'm sitting here wondering -- maybe I missed it. But when we -- if this was moved off an abbreviated schedule and into a more detailed phase, why did that happen? And -- but, I mean, from what I've seen, I concur, but I'm wondering whether I --

DR. MURPHY: You just want to make sure there's something -- yeah.

DR. ROSENTHAL: Did I miss something?

DR. MURPHY: No, you didn't miss anything. Okay, one individual on the committee had a specific question about the presentation you were just given. Instead of -- and they felt it was an appropriate opportunity to educate the committee on how these products are developed for infants and neonates, and so that was -- and it doesn't matter what the issue is. If any committee member raises a question by the process that was defined, it has to go back to a full review, and that's why. You didn't miss anything.

DR. ROSENTHAL: I enjoyed the -- and I mean it was helpful, but that's helpful as well. Thank you.

DR. MCGOUGH: Jim McGough, I concur.

DR. SANTANA: Victor Santana, I concur.

DR. REED: Michael Reed, I concur.

DR. MINK: Jon Mink, I concur.

DR. CNAAN: Dr. Cnaan, I concur.

KYTRIL INJECTION (GRANISETRON HYDROCHLORIDE) AND A CLASS REVIEW
OF 5-HT₃ RECEPTOR ANTAGONISTS

CHAIRMAN TOWBIN: Very well. So it sounds like we have concurrence and we can move on. Our next presenter related to Kytril, I believe is Dr. Snyder, who is a medical officer on the pediatric and maternal health staff within the Office of New Drugs. Dr. Snyder received her medical degree from the University of Virginia and did her internship and residency at the University of Maryland, and was chief resident at Sinai Hospital in Baltimore, completed a pediatric academic development fellowship at Johns Hopkins Hospital. She is board certified in pediatrics, and a fellow of the American Academy of Pediatrics, and spent time in pediatric private practice, has consulted for the pharmaceutical industry, and the National Institutes of Health. Just prior to coming to the FDA, she worked as a consultant to an IRB in the area of human subjects protection and research ethics, serving as an IRB chair for three years, and lived to tell the tale. She recently joined the FDA in April of 2012.

DR. SNYDER: Thank you. All right, I'm presenting the pediatric focus safety review for Kytril or granisetron hydrochloride, and here's the format for this presentation. This presentation includes a class review of the 5-HT₃ receptor

antagonist -- I'm sorry. This is what happens when you're short. [laughs] Kytril's an injection for interventions infusion that was originally approved in December, 1993. Kytril is serotonin 5-HT3 receptor antagonist. A pediatric labeling change in April 2011 triggered this PAC presentation. The sponsor, Hoffmann La Roche, is in the process of discontinuing Kytril for reasons that are not related to safety. Granisetron will still be marketed in oral and IV forms as a generic and under the trade name of Sancuso, a transdermal form of the drug. Sancuso has a post marketing requirement for pediatric studies. Kytril's approved for the prevention of nausea and vomiting associated with chemotherapy in adults and pediatric patients ages two years and above. Kytril is indicated for use in adult patients for prevention and treatment of post-operative nausea and vomiting. There's an outstanding post-marketing requirement for a study to assess the risk of QT prolongation. A pediatric study was conducted in 157 patients ages 2-to-16 years, at two dose levels to assess intravenous granisetron in the prevention of post-operative nausea and vomiting, or PONV. The trial did not have an active comparator. QT prolongation was seen at both dose levels and efficacy was not established due to a lack of dose response. Although the study fulfilled the post-marketing requirement, the data did not support adding the pediatric indication to the labeling.

Now we'll move on to pediatric labeling changes and relevant labeling. In the use and specific population section, the pediatric use subsection was updated to include the information on the pediatric studies that were done on PONV. This subsection states that safety and effectiveness in PONV has not been established in any pediatric population. As we look at other areas of labeling, note that pediatric information on the approved indication of chemotherapy induced nausea and vomiting, or CINV, is sprinkled throughout various areas of labeling. On this slide you see that information is included in dosage administration and warning and precautions. Since benzyl alcohol is added as a preservative to the IV formulation, the risk to neonates of gasping syndrome is included. We already looked at the information of PONV added to the pediatric use section in an earlier slide. The information on CINV and benzyl alcohol risk exposure in the IV preparation is also included under pediatric use. These areas are cross reference to other areas of the labeling. This section states that Kytril has been approved for ages 2-to-16 years for CINV, but that safety and effectiveness have not been established under age two. The clinical pharmacology in the clinical studies section include the pediatric study information that supported approval on CINV.

Now we'll move on to drug use. This table provides the total number of patients for granisetron IV use in the U.S.

inpatient and outpatient retail pharmacy settings. Pediatric patients age zero-to-16 years accounted for 4 percent of total patients for the review period. Of that 4 percent, 93 percent of patients were two years of age and older. Now, we'll move on to the adverse events reports. This table includes the adverse events reports submitted over the 19.5 year time period from the date of approval to July 31st, 2012. There are 1,138 reports. Of the 1,138 reports, 46 were pediatric. There were seven pediatric deaths. Review of the 165 unknown age reports did not identify any pediatric deaths. Of the total 46 pediatric reports seen on the previous slide, there were 15 duplicate reports. Ten reports were excluded because the outcome was not serious or the report was not related to granisetron. This resulted in a total of 21 pediatric cases for analysis, including the four deaths. Here are the characteristics of the cases, broken down by age, serious outcome, indication, and duration of therapy. The majority of the cases were identified in the approved age range of 2-to-16 years, with two cases under age two. There were four deaths, as already discussed, six hospitalizations, four life threatening events, and seven cases classified as other serious outcome. Most of the cases were identified in the approved indication of CINV and the main duration of therapy was 15 days with a range of one to 150 days.

Now we'll move on discussing the four deaths. Note on

this slide and on subsequent slides, unlabeled events are underlined. The deaths on this slide were all on patients treated with granisetron for CINV. The first patient was a ten-year-old female who died from pulmonary fibrosis. This patient was on several chemotherapeutic agents, including cyclophosphamide, which is labeled for pulmonary fibrosis. The second patient died of heart failure. This patient's autopsy results showed evidence of myocardial infarction. The patient was on cisplatin and vincristine, both labeled for MI. The third patient died of anaphylactic shock while being treated with vincristine and cyclophosphamide in addition to granisetron. These chemotherapeutic agents are labeled for anaphylaxis. The last step was an 11-year-old female with mucositis who had a recent bone marrow transplant. The patient was on granisetron, multiple chemotherapeutic agents, and Fentanyl. The patient developed confusion with visual hallucinations, marked anxiety, tremulousness, ataxia, and mild clonus two weeks later. This case was interpreted to be a case of serotonin syndrome. Symptoms of serotonin syndrome were solved with discontinuation of granisetron and Fentanyl, a reported serotonergic agent. The patient died six weeks later of renal and hepatic failure related to veno-occlusive disease. We will discuss this case again in the class review of 5-HT₃ receptor antagonists.

Before moving on, I thought I'd present some information on serotonin syndrome. Serotonin syndrome is a predictable consequence of exposure to a serotonergic agent. Serotonin syndrome may present in mild or severe forms, and can occur within minutes of exposure to a precipitating agent. The criteria include a history of exposure within the last five weeks in one of the following categories; spontaneous clonus, inducible clonus in either agitation or diaphoresis, ocular clonus in either agitation or diaphoresis, tremor and hyperreflexia, muscle rigidity, temperature greater than 38 degrees centigrade, and either ocular or inducible clonus. These criteria described are referred to as the Hunter criteria. Treatment includes removal of the inciting agent and supportive care. Here's a schematic drawing showing -- that illustrates the spectrum of symptoms. Here's a list from the literature of some of the drugs that have been reported to be associated with serotonin syndrome. As you can see, there are a large spectrum of drugs associated with this disorder. Drugs of abuse are not included here, but have been reported to also be associated with serotonin syndrome. Now that you are all familiar with some of the features of serotonin syndrome, I'll describe four non-fatal cases of serotonin syndrome that were seen with granisetron. Again, not on this slide and on subsequent slides that unlabeled events are underlined. There are four cases reported. The two

cases on this slide were patients, a two-year-old and a five-month-old, who were also on tramadol, a drug that's labeled for serotonin syndrome. In both these cases the event was reported as a seizure, but further review of the cases indicated that the symptoms met the criteria for serotonin syndrome. The next two cases, a seven-year-old and a three-year-old were on granisetron for chemotherapy prophylaxis. In both cases, the symptoms reported, as outlined on this slide, were considered to be possible cases of serotonin syndrome, and occurred within hours of receiving the drug. In both cases, the patients -- the patients had received granisetron with previous doses of chemotherapy. In the second case, the symptoms reportedly resolved eight hours after the medication was stopped. The remainder of the adverse events for granisetron were detected in patients who were being treated for CINV. Of the 13 reported adverse events, four were unlabeled. These unlabeled events were ileus, deep vein thrombosis, pancytopenia, and skin necrosis with bullous dermatitis. These events occurred only once over a 19 year review period in patients whose medical history was complicated by underlying disease and by the use of other medications.

As a result of the pediatric focus safety review of adverse events reports for Kytril, serotonin syndrome was identified as a potential unlabeled safety signal. This

prompted a review of the potential for serotonin syndrome to occur with the use of other 5-HT₃ receptor antagonist drugs. No other safety signals were identified.

Now we'll move on to the class review. Here are the four 5-HT₃ receptor antagonists that were include in this review. Information on approval on pediatrics is included on the slide as well. I'll give you a moment to review this information. Here is some information on the use of these products. This graph illustrates the national sales for 5-HT₃ receptor antagonists for all formulations from manufacturers to all U.S. channels of distribution annually. Sales increased by 85 percent from the year 2007 to the year 2011. Ondansetron products accounted for 96 percent of total sales in the year 2011. This graph illustrates the number of pediatric patients for 5-HT₃ receptor antagonist regardless of formulation, and the inpatient, and outpatient, and emergency room settings annually. In the year 2011, approximately 2.1 million pediatric patients were billed for ondansetron. Ondansetron accounted for 99 percent of total pediatric patient use in the year 2011. This graph illustrates the number of pediatric patients for granisetron, palonosetron, and dolasetron in the inpatient and outpatient emergency room settings annually. In the year 2011, there were 1,200 pediatric patients age 0-to-16 years who were billed for granisetron, a 72 percent decrease in patients from

4,300 patients in the year 2007. New safety language is added to the dolasetron label in May, 2007, which cautioned against pediatric use among patients with a history of QTC prolongation. However, further in depth analyses are needed to establish a cause for this decrease in use.

A fair search was done in order to determine if there was an association of serotonin syndrome with 5-HT₃ receptor antagonist use. In order to identify a case, the case needed to be coded as a case of serotonin syndrome, or needed to have symptomatology that matched the Hunter criteria. Additionally, a serotonergic agent must have been suspect or listed as a concomitant medication. Other diagnoses with similar symptoms were excluded. Here is the adverse event case selection for serotonin syndrome. Of a total of 137 reports, there were 78 duplicate reports, 20 reports were excluded because they did not meet the case definition, or were not temporally related to the drug, or were not informative. This resulted in the total of 39 cases for analysis, including four deaths. Note that these cases included adult and pediatric cases. Here are the characteristics of the cases that met the case definition. The frequency of the reported cases match the drug use information reported earlier in that most cases were seen with the drug with the most used ondansetron. In 26 case the use of another serotonergic agent was reported along with the 5-HT₃ receptor

antagonists. Cases range from ages one year to 80 years. Most of the patients were treated for CINV or PONV.

Now we review the three reported deaths. The first case with a 30-year-old male with malignant melanoma who received ondansetron during a chemotherapy session. The cause of death was cerebral necrosis secondary to status epilepticus. However, after the chemotherapy session, the patient became confused, was comatose, and developed agitation, mydriasis, and signs of autonomic overdrive. Reported symptoms were consistent with serotonin syndrome. The patient was also on Fentanyl, a reported serotonergic antagonist that may have contributed to the presentation of symptoms of serotonin syndrome. The second case was a 69-year-old female that developed serotonin syndrome after undergoing surgery. The patient was initially diagnosed with malignant neuroleptic syndrome, possibly because of exposure to a [unintelligible] of drug that may trigger this particular syndrome. However, the patient was on multiple serotonergic agents. A diagnosis of serotonin syndrome was made after the patient died, with further review of the case by the reporting physician. The specific symptoms were not included in the case report. The third case was previously discussed in the pediatric focus review of Kytril. As mentioned before, this 11-year-old patient recently had a bone marrow transplant and developed serotonin syndrome two weeks after exposure to

granisetron, and Fentanyl, and several immunosuppressive agents. Symptoms included confusion with visual hallucinations, marked anxiety, tremulousness, ataxia, and myoclonus. The symptoms resolved after discontinuation of granisetron and Fentanyl. As previously stated, the patient died of renal and hepatic impairment secondary to veno-occlusive disease six weeks later. We also thought it would be helpful to discuss the best representative case. This was a 69-year-old female who developed serotonin syndrome after receiving ondansetron for PONV after knee surgery. This patient received oxycontin after surgery, but was also on a monoamine oxidase inhibitor, phenelzine. Both these drugs have serotonergic properties. The patient developed drowsiness, confusion, agitation, hallucinations, hypertension, and fever within hours of exposure to ondansetron. The symptoms resolved within five days of discontinuation of ondansetron and oxycontin for supportive care chlorpromazine for agitation. The last case is a representative overdose case. This case occurred in a 12-month-old infant who was not on any other drugs at the time of the event. This infant ingested somewhere between 56 to 64 milligrams of ondansetron. For comparison, the average recommended IV dose for a one-year-old would be 1.5 milligrams and the recommended oral dose for a 4-to-11 year old would be 4 milligrams. This patient became somnolent and developed myoclonic movements of

the extremities within 20 minutes of taking the drug, and then progressed to other symptomatology that was consistent with serotonin syndrome. The event led to seizures and intubation. The patient received activated charcoal and supportive care, and fully recovered, and was discharged within 48 hours.

This concludes the pediatric focus safety review for Kytril and the 5-HT3 class review of serotonin syndrome. Both the pediatric focus review and the class review identified a potential risk of serotonin syndrome with 5-HT3 receptor antagonists alone and when used in combination with other drugs. No other potential safety signals were identified. FDA is working with sponsors to update the product labeling for 5-HT3 receptor antagonist to include the potential risk of developing serotonin syndrome. Does the committee concur? And thanks to all the people on this slide for their help with this review.

CHAIRMAN TOWBIN: Thank you very much, Dr. Snyder.
Dr. Dracker.

DR. DRACKER: I just have a couple questions, and this was a great presentation, because we're -- clinically we use, you know ondansetron like water. Why, I think I prescribe more than amoxicillin at this time of the year. But regardless, the two issues that come out and were obvious was the use of opioid like substances, whether, you know, synthetic or non-synthetic, and a concomitance of, you know, adverse reactions and deaths

associated with that. And the second is the deaths that occurred were patients who had malignancies, or were on a number of drugs, and have probably some degree of impairment of liver dysfunction as well. And whether those -- you know, in your recommendation to the manufacturer, are those issues that are being brought forward.

DR. SNYDER: Okay. Does division want to comment on that?

DR. BERRY: Yes, my name is Karyn Berry. I'm a medical officer in the Division of Gastroenterology and Inborn Errors Products. So yes, we are currently -- once we receive this information, we currently are reviewing and discussing internally where we're going with this, and how to best notify, and make clinicians aware, if we need to do, how we need to do it. So as part of that, we will also be looking at the pharmacokinetics, pharmacodynamics, including all of that in the evaluation that we're doing to try to assess how do we move forward with this.

CHAIRMAN TOWBIN: Can you say a little bit about how the decisions that you reach will come back to this committee, because I think people might be interested in what you decide to do; that is, how you inform people, and the language that you use, and so on.

DR. BERRY: Typically, once we do make the decision,

and if we do decide to make labeling changes, then that information will be relayed to clinicians through various communication mechanisms, so that information does get out. And that will be a standard procedure that we do use.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: Quick question. So the labeling changes that are being considered, are these being considered in the pediatric sections specifically or just in the overall label? And sort of a corollary question is, is the risk of serotonin syndrome different in kids in general than it is in adults?

DR. HAUSMAN: Hi, this is Ethan Hausman. The differential risk between the occurrence of this and kids and adults, there's insufficient information at this time to address the questions. So I have no answer for the committee. There are several parts of the label that may be affected. That's going to be a question that's going to -- the answer will get clarified based on work that OMD does when -- complete their investigations with the pharmacodynamic and pharmacokinetic questions, so I'm now going to defer back to the division.

DR. KORVICK: I'm Dr. Korvick -- is this on? I'm Dr. Korvick from the Division of Gastroenterology and Inborn Errors Product; I'm the deputy director for safety. And we were made aware of this signal through the OSE review, and currently we

are gathering our other experts. And you did point to the two areas that we were very interested in. The potential for drug/drug interactions. As you know, this is metabolized by the liver in the [unintelligible] system, and so were a lot of those other drugs that are already known to cause this, and we're also looking into see if there is any kind of mechanistic interaction. So we have gathered together what we call a track safety issue team, and we've notified all the sponsors of such, and so in that what we do is disassemble additional experts in our division, OMD, and other corollary divisions, to work out exactly what we think this signal means, and how it can be interpreted. So, actually we're in early days of that and I would leave it up to Dianne and that team to say how it will come back to you. But as we try to elucidate the mechanisms, et cetera, then the team will recommend the appropriate places in the label to put this information, and we will further be discussing with our communication colleagues in the agency as to how to best communicate this to the public. And then, I guess, again, Dianne can talk about how this would best be brought back to this committee.

CHAIRMAN TOWBIN: Dr. Murphy.

DR. MURPHY: A couple of things. You can tell sometimes that the committee will get something where the reviews have brought up an issue, and we have not reached the

finish line, okay, but we don't want to come to this committee and tell you nothing, because it makes it look like we're going to present you all this data and we're going to say like, we're not doing anything. Obviously we are very actively reviewing this. So that's the situation. And the division is looking at some of these other issues that might impact what the warning would be, or what the recommendations on the label would be. I think if you have some specific recommendations that you are concerned about, you should voice those also, but as far as it coming back to the committee, I think you can request that we bring you an update, and it's a common thing for you to do. If you have any other concerns that you -- others want, you can express those, too. But it's very common for the division to get the labeling done, and then we put it on a list to bring back, follow-ups, if that's what you request. If it's a routine thing, some minor thing that the division's doing and it's not very complicated, sometimes you all will request it, we just send it to you, and that you don't need to have it presented to you. So those are some of the options. I mean, the ultimate option was you'll look for it in the mail or in the news, but that's the spread that I can offer you.

DR. KORVICK: Doc, to compliment that, I think that we'd be interested in any comments that you have to make about what you saw today and what your concerns might be, as we work

on this project. Thank you.

CHAIRMAN TOWBIN: Dr. Mink, did you want to say something?

DR. MINK: Just a question that isn't directly pertinent to the question about labeling, but -- these are serotonin -- largely peripheral serotonin receptor antagonists. Any idea why they would lead to a syndrome that's usually associated with excess serotonin? I don't doubt -- I mean these are the symptoms that I've seen in this and there -- but there are concomitant medications. Is it thought that there may be some other mechanism of action of these drugs?

DR. HAUSMAN: Yeah, Ethan Hausman again. There -- we face the same question, and there is a theory which is not -- it's a theory; it's not substantiated by a lot of data. But I guess it's theoretically possible, that's been published, that as a serotonergic blocker effects 5-HT₃ mechanism, there may be some increase sensitivity of the other serotonergic receptors. So one theory is that the other receptors get more sensitized, so if there's another serotonergic agent floating around, even though you have a serotonin blocker, it may increase your chance of getting serotonin syndrome.

CHAIRMAN TOWBIN: Dr. Mike LaRussa, I think was next, and then Dr. Dracker.

DR. MURPHY: Just to say that I want to reflect that

there was quite a bit of discussion about your question as to why this is. It's been reflected.

DR. HAUSMAN: And additionally, while most of the cases were actually seen with nominally confounding agents that are risk for serotonin syndrome themselves, the two overdose cases were without any other drugs. And granted, they were overdoses so we wouldn't expect patients to be exposed to that kind of level of the drug. There were no concomitant medications and those descriptions were very clearly consistent with serotonin syndrome.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: So I wanted to ask about the overdose cases and you presented a representative case. Did any of the other serotonin syndrome cases involve overdose and if so, were there any patterns of why the overdose occurred that might be informative and might require some change in product labeling?

DR. SNYDER: I think that Christian has that information.

MR. CAO: Hello. My name's Christian Cao. I'm a reviewer from OSE who did -- primary author in this -- both documents, the Kytril and the class review.

In regards to your question regarding were there other overdose cases, there were two overdose cases and both were with Ondansetron and it was in both pediatric patients and they were

exposed to medication inadvertently because the child was able to open the medication bottle that was for the parents. So there was no other medication -- I'm sorry. There was no other 5-HT3 antagonist overdose cases in adults.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: It's very interesting to think that this is probably almost like a tachyphylaxis syndrome that's occurring that you see with other drugs as well. And the other issue is it's not necessarily overdose; it may be overuse, which we find very common with this medication, that they're using it when the child is -- are vomiting, they give the dose more frequent than they really should be doing so and we have no way to know that. The other thing I wanted to mention is that the most common use of this drug is in emergency rooms. There's not a child that leaves an emergency room -- I shouldn't say that uniformly but in general -- that doesn't get put on Zofran and as well as pain medication sometimes like we referred to. And I think -- I don't know if it's possible -- should even a warning go out, before you finish I think an excellent review of what you're doing, to the emergency rooms to say, you know, be very cautious in how you're using this drug, especially if you're going to use in opioid-like drug along with it upon discharge.

CHAIRMAN TOWBIN: Dr. Reed.

DR. REED: Thank you. I'd just like to come back to the pharmacodynamic component and one, not as -- not everything is all or none relative to penetration into the CNS and as we know, you know, the vomiting center does have serotonin receptors at the base of the brain and so, some drug is getting there. Further, I would -- you might also think about receptor occupancy that it now allows more circulating serotonin that may factor into this. But I think when you look at this class of drugs, it was the other class that was -- all the other classes that were shown on that slide. Serotonin syndrome relative to a dose or some other concurrent drugs, et cetera, is quite logical.

CHAIRMAN TOWBIN: Other comments? All right. Well then, I think we -- Dr. Rosenthal.

DR. ROSENTHAL: So I've learned almost everything that I know about developmental changes in metabolism from Dr. Reed and others on this committee but the one thing that I would say is just in looking through the materials, it looks like these agents are metabolized by the cytochrome P450-3A isoforms and I recall from previous meetings that there are pretty pronounced developmental changes in those metabolic pathways. And so, the only thing that I would say is that I would hope that the labels would sort of be sensitive to those changes because some of the -- some of the adverse events may be particularly pronounced in

younger kids and as these drugs are used more and more in younger kids, I think that's an important point.

CHAIRMAN TOWBIN: So Dr. Murphy indicated that if we wished to hear back about the progress on this or wish to review labels or anything of that sort, we need to say so. And so, perhaps if people had some thoughts about that when we come to voting, that could be a useful thing to add in.

DR. MURPHY: And when you vote, if you have a recommendation like some of you did, would you please just restate what it is that you hope the agency will be looking at or will comment on or give information to when we go around for the vote. Thank you.

CHAIRMAN TOWBIN: I am not a voting person but I would like to say that I did look at the label and I had some concerns, particularly in the highlights section. I was impressed that in the drug interactions segment, the concerning interactions are the end and the things that are not interactions are the things that it opens with and I thought that was sort of converse reasoning. And also that if it does look as if there is going to be an interaction here with other agents that we might want to be specific about it.

The other thing is that this notion of the benzyl alcohol and gasping syndrome -- there's only a reference to benzyl alcohol in that highlights section and no comment at all

about why that would be a problem and so, maybe that language could be expanded so that people would understand why that would be concern. So I think with that, we might be ready to have people say what their wishes are. Ms. Celento.

MS. CELENTO: Amy Celento. I concur and I would like to see this again for many of the reasons presented here. Thanks.

DR. WIEFLING: Bridgette Wiefling, I concur.

DR. WAGENER: Jeffrey Wagener. I agree.

DR. GLASIER: Charles Glasier. I concur.

DR. FRANCO: Israel Franco. I concur.

DR. DRACKER: Bob Dracker. I concur; however, I would definitely like to see, once all your work is done, the presentation of that information. I also would like to see if you can consider a warning notification to go out as far the concomitant use of certain medications, especially if there are patients, which I am aware of, that are impaired P450 metabolizers.

DR. LARUSSA: Philip LaRussa. I concur, but I would also like to hear back from you, especially about concomitant medications.

DR. CATALETTO: Mary Cataletto. I concur and would also like to hear back from the group once those studies are completed.

DR. HUDAK: Mark Hudak and I concur with the comments as well.

DR. BAKER: Susan Baker. I concur and I would like to have further information once your work is done.

DR. WHITE: Michael White. I concur and in reviewing the labeling, we're using an awful lot of this stuff in children for no labeling available.

DR. ROSENTHAL: Geoff Rosenthal. I concur and this is the kind of thing where I think, in my history with the committee, it's useful to have it come back in some form. I'm not sure that -- it may be adequate to have people just reflect on the labeling changes that are being considered and not necessarily presented in open forum unless there's some disagreement about the way that the label reflects potential risks in kids.

DR. MCGOUGH: James McGough. I concur.

CHAIRMAN TOWBIN: If you don't mind, Dr. Santana had to step away for just a moment and before he did, we got his vote and he said that he concurs with follow-up to the Pediatric Advisory Committee.

DR. REED: Michael Reed. I concur as well and I agree with the comments that were made regarding the follow-up.

DR. MINK: Jon Mink. I concur, both with the follow-up and the recommendation.

DR. CNAAN: Avital Cnaan. I concur with the recommendation and would like to see the follow-up. Thank you.

CHAIRMAN TOWBIN: Yes. Dr. Yao.

DR. YAO: Yeah, I just wanted to clarify your comment about the gasping syndrome.

CHAIRMAN TOWBIN: Yes.

DR. YAO: So that was -- are you referring to the Section 8.4 Pediatrics that there's just one sentence? Yeah. So, if you refer -- it refers back to the warning section and there's a very, very detailed description there and we typically --

CHAIRMAN TOWBIN: I did note that.

DR. YAO: Yeah. Okay.

CHAIRMAN TOWBIN: But I still that in the highlights, it's a little like practitioners going to this will probably need a little bit of a stronger tag, in my humble opinion, to look to that section because otherwise, it just isn't meaningful, I think, to many people.

DR. YAO: I see. So your concern is in the highlights section. Okay --

CHAIRMAN TOWBIN: Correct. You're exactly right.

All right. So, it sounds as if there is a general view that people would like to hear back about this as you reconsider labeling changes and information related to some of

the studies that are underway and I thank you very much for providing this early information to us.

I think that we're ready now to talk about esomeprazole. Dr. Reed will be recused from the discussion of Nexium and Dr. Taylor is rejoining us to offer the presentation.

NEXIUM (ESOMEPRAZOLE MAGNESIUM)
& NEXIUM IV (ESOMEPRAZOLE SODIUM)

DR. TAYLOR: I will be presenting information on Nexium I.V. and Nexium orals formulations. This is an outline of the information I'll be presenting today.

Just some background information about the drug. Nexium or esomeprazole has several formulations: a delayed release oral capsule, delayed release for oral suspension, and intravenous formulation. It is a proton pump inhibitor. It is manufactured by AstraZeneca. The original market approval was February 20, 2001 and it was granted exclusivity in May of 2009.

The indications first for oral Nexium for both pediatric and adult patients: the treatment of gastroesophageal reflux disease or GERD, healing of erosive esophagitis, and symptomatic GERD. In patients one month to less than one year old, only for erosive esophagitis due to acid-mediated GERD and it is not indicated in patients less than one month. For adults, you'll see that there are a few other indications that are not approved in pediatrics.

For Nexium I.V., it's for the treatment of GERD with erosive esophagitis in adults and pediatric patients greater than one month of age when oral therapy is not possible or appropriate.

This next couple of slides goes through the pediatric studies that were done for Nexium oral, first, and then for I.V., and what I've also done is indicated by each age group and, in some cases, indication when this actually was put into the labeling, so those are the dates you see there.

So in patients 12 to 17 years old, there was a pharmacokinetic study in 28 patients and a randomized double-blind parallel group study in 149 adolescent patients with clinically diagnosed GERD that was conducted to evaluate the safety and tolerability. Efficacy was extrapolated from studies in adults and this was labeled in April of 2006.

In the age group one-to-11 years, there was a pharmacokinetic study in 21 patients and a parallel group study in 109 patients with a history of endoscopically-proven GERD conducted to evaluate safety and tolerability. Efficacy, again, was extrapolated from studies in adults and this was placed in the labeling in June of 2009.

For one month to less than one year, esomeprazole was not shown to be effective for the treatment of symptomatic GERD in 98 patients and the information from that study was labeled in June of 2009.

The use of Nexium in pediatric patients one month to less than one year of age for treatment up to six weeks of erosive esophagitis due to acid-mediated GERD was supported by

extrapolation of results from adequate and well controlled studies for adults and safety, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients. And this information was placed in the labeling in December 2011. For neonates, a pharmacokinetic study was conducted and labeled in June of 2009.

For I.V., the use of Nexium I.V. for injection in pediatric patients one month to 17 years of age for short term treatment of GIRD with erosive esophagitis is supported by results from a pharmacokinetic study on Nexium I.V. performed in 50 pediatric patients. Also, predictions from a populated -- population PK model comparing I.V. PK data between adults and pediatric patients. Also, the relationship between exposure and pharmacodynamic results obtained from adult I.V. and pediatric oral data. And then, PK results already included in the current approved labeling and from adequate and well-controlled studies that supported the approval of Nexium I.V. for adults. So all of these went together to be able to support the indication in pediatric patients and that was placed into the labeling in April 2011.

Just some recent pediatric labeling change related to this particular safety review for oral Nexium. The indication and usage section under treatment of GERD, we placed into labeling that in infants one month to less than one year, Nexium

is indicated for short term treatment up to six weeks of erosive esophagitis due to acid-mediated GERD. In the dosing and administration section, a dosing chart was updated to include weight-based dosing for one month to less than one year for erosive esophagitis due to acid-mediated GERD. In Section 8, Use in Specific Populations, Section 8.4, Pediatric Use, a statement was included describing the support for the use of Nexium in pediatric patients one month to less than one year of age, again, for erosive esophagitis due to acid-mediated GERD. And in Section 12, Clinical Pharmacology, pharmacokinetics in patients one to 11 months are described.

In Nexium I.V. in the labeling, again, in Section 1, Indication and Usage, the age was expanded to include pediatric patients one month of age and older. In dosage and administration, we added dosing recommendations for pediatric patients one month to 17 years.

In the pediatric use subsection, it describes the supportive data for use in pediatric patients, again, one month to 17 years for short term treatment of GERD with erosive esophagitis. And in Section 12, the results of a pharmacokinetic study in 50 patients, age zero to 17 years, in pharmacokinetic analysis are described.

The relevant safety labeling in the contraindications section, Nexium is contraindicated in patients with known

hypersensitivity to PPIs. In the warning section, we have warnings about atrophic gastritis, clostridium difficile, bone fracture, hypomagnesemia, concomitant use with -- of Nexium with St. John's wort or rifampin, and also concomitant use of Nexium with methotrexate. In adverse reactions in the oral labeling, in 98 patients one to 11 months old, most frequently reported adverse reactions are listed here. In the one to 11 year old, again, the most frequently reported reactions, at least 1 percent, are listed here and then also in the adolescent patients. And these are from the clinical trial experience. With the I.V., there's a statement saying it's consistent with the known safety profile of esomeprazole and no unexpected safety signals were identified.

So this product has been presented previously to the Pediatric Advisory Committee. In June -- the first time in June 11, 2002, the committee discussed the PK, PK/PD, and efficacy studies in neonates and infants less than one year and this included a discussion on the extrapolation of efficacy from adults, the study design, and also the efficacy end points. The drug was then brought back to the Pediatric Advisory Committee in June of 2010 and at that time, there was a safety review of four PPIs that included Nexium. And at that time, the committee concurred with continuing standard ongoing safety monitoring but

they did ask for a review in one year. And the committee was given an update on the KidNet pilot study in 2012.

And then just -- this was not the Pediatric Advisory Committee although there were some members from the PAC that were -- that participate in this. But the Gastrointestinal Drugs Advisory Committee discussed the PPIs and discussed clinical trials of PPIs in patients less than one year. It was noted that the pathogenesis of symptoms is different than in older pediatric patients and also that studies in less-than-one-year olds should be required for acid-suppressing agents in pediatric patients with acid-mediated disease.

So now I'm going to go through a few slides about the use information. This first slide includes both I.V. and oral and gives you information about the total use from June 2005 through May of 2012 and you'll see the pediatric numbers in -- highlighted in red there.

This is with -- for I.V. esomeprazole and what it does is just give you a graphic representation and the data are broken down by year. And you'll see the lines represent different -- the different age groups: adolescent, one-to-11 year old, and less than one year. And then, this is the same information, only for oral esomeprazole. As far as the top prescribing specialties, general practice and family medicine were the top prescribing specialties for all prescriptions of

esomeprazole and that was 35 percent of prescriptions.

Pediatricians accounted for less -- for approximately 2 percent of prescriptions. The top diagnosis code in pediatric patients was esophageal disorder.

So now, I'll get to the adverse event reports. You'll see here circled in red the pediatric reports for oral suspension. There were two serious adverse events and no deaths. If you look at what our -- how we went through the case selection, we had two serious reports, then we looked at whether or not there were any duplicated reports, which there weren't, and then, there were no reports that needed to be excluded once they were reviewed and so, our case series is n=2.

For I.V. Nexium, the -- you'll see here circled in red the pediatric -- there were six pediatric serious adverse event reports and two deaths. Again, going through the same exercise, we came out at the end with a case series of six that included the two deaths. So I just want to review those two pediatric deaths that were found reported under Nexium I.V. There was a 16-year-old male with a history of heroin and cocaine addiction, was admitted for multiple drug intoxication and overdose. And you'll see the drugs that he had there. He suffered worsening pulmonary complications, deterioration of hepatic function, and hematologic abnormalities. Esomeprazole I.V. was given along with other supportive interventions and the patient died of

vasoplegic shock. The second case involves an eight-year-old female who was described as very weak with HIV infection. She was admitted for aspiration pneumonia. She could not eat and had blood in her stools. No other prior medical or pharmacotherapy information was available in the report. Esomeprazole I.V. was given for one day. The patient later died of unknown causes. The time course from Nexium -- the administration to death cannot be determined.

Now I'll just give you a summary of the serious nonfatal adverse events for both oral and I.V. Those events that are unlabeled are underlined. And you see here under I.V., the unlabeled adverse events are pulmonary deterioration, respiratory distress, bullous epidermolysis, cytotoxic edema, hemiplegia, facial palsy, and seizure.

So this concludes the pediatric-focused safety review. No new safety signals were identified and we recommend continuing routine monitoring. We ask, does the committee concur? And I just want to acknowledge the following people for their help with this presentation.

CHAIRMAN TOWBIN: Thank you very much once again, Dr. Taylor. Dr. Rosenthal.

DR. ROSENTHAL: Thank you for your presentation. So I'm -- you know, I'm recalling other PAC meeting discussions about the proton pump inhibitors in reflux, and I'm looking at

the label that came with the package. And specifically, you know how on the very first part of the label, there is the indications and usage in bulleted form. It's sort of the highlights of the indications and usage. So in that section, there's no reference made of treating esophagitis due to acid-induced gastroesophageal reflux, which was the indication that I recall we sort of ended up with in pediatrics rather than symptomatic GERD. Now, you know, down farther in the label in the more -- in the better developed indications and usage section in 1.1, most of what's discussed is erosive esophagitis but that's not -- that's not actually up in the bulleted indications in the top. And there's just a, you know, pretty fleeting mention that there's not a GERD indication in smaller infants and -- but I actually think that that was an important output from the discussions and deliberations that have come before this committee because I think the studies that were shared with us did fairly convincingly show that these -- that proton pump inhibitors as a class and this drug as well were not effective for treating symptomatic GERD in very small infants.

CHAIRMAN TOWBIN: Dr. Mink.

DR. MINK: Just for my information, back in Slide 7, where you talked about indications for oral -- and this follows up on the previous question, too. It's stated that it was not shown to be effective for treatment of symptomatic GERD in one

month to less than one year, but the labeling for use in erosive esophagitis is based on extrapolation from adult studies of efficacy. And I'm just wondering what the -- what the procedure is at the FDA and what the rationale is for a labeled indication based on extrapolation from adults in a age range where a related indication has been shown not to be effective -- or related uses been shown not to be effective in children of that age. I understand the safety data are reassuring but in terms of efficacy data, what's the rationale for extrapolating from adult data in that very young age range for the erosive esophagitis?

DR. FIORENTINO: Well, I -- this is Rob Fiorentino, Gastroenterology at the FDA. That -- I mean, this actual program, an approach came out of a discussion that occurred at an advisory committee meeting that I believe occurred --

DR. WYNN: In 2010.

DR. FIORENTINO: -- a couple years ago -- 2010, which allowed or agreed that this extrapolation approach could be applied. Dr. Wynn, yeah.

DR. WYNN: My name is Erica Wynn. I'm one of the clinical reviewers.

CHAIRMAN TOWBIN: Thank you.

DR. WYNN: I did not review the oral Nexium but I did do the I.V. Nexium and basically, originally, this application

was -- received a complete response because of the lack of efficacy but as Dr. Fiorentino has said, when the GIDAC came back in November 2010 and said, for those pediatric patients with endoscopically -- [clears throat] excuse me -- with endoscopically diagnosed erosive esophagitis, the course of disease and the treatment were the same for adults and pediatric patients such that the extrapolation was appropriate if there were PK and PD data available. Subsequently, after the GIDAC, the company came back and asked for that small subpopulation to get the indication. So that's why you see that it was labeled in 2009 -- it's not exactly correct.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: So I think -- what I recall regarding the discussions about extrapolation of efficacy in -- for this class of drugs was that I think there was some data that showed acid suppression, even in young infants, if I'm remembering this correctly. And so, I think the -- as the discussion went, that if we truly believe there was acid-mediated disease, then it was probably reasonable to extrapolate efficacy for acid-mediated disease. But at the same time, there was a fairly robust discussion that most gastroesophageal reflux disease in infants is not an acid-mediated phenomenon. So, you know, I think great pains were taken in those meetings to try and distinguish between what is a very common syndrome, GERD, in infants, and

what is a very rare occurrence, which is acid-mediated esophagitis in infancy.

CHAIRMAN TOWBIN: Dr. Baker.

DR. BAKER: This is Susan Baker. I had a couple questions for you. On Slide 26, at the end, you say "lack of efficacy." What do you mean, "lack of efficacy?" For the erosive esophagitis or lack of efficacy under year of age or -- it's -- I just wasn't sure what the take-home message from that was. And then I had another question on the actual labeling. I think this has been brought forward before, but if you are extrapolating studies in adults that referred only to endoscopically or histologically proved reflux esophagitis -- I don't know which one. I'm assuming it's endoscopic and you're using the LA classification, is that correct? Then don't you want to say that? Because the inference is that it's -- you can just give it to kids. So those are my two questions.

DR. HAUSMAN: The response to the lack of efficacy here -- this is Ethan Hausman. Lack of efficacy here is how the adverse event report was received.

DR. BAKER: Okay.

DR. HAUSMAN: So we do not have the information for all the questions you have, as good as that information would be to have; it just came in as, drug didn't work.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: Yeah. Quick question. I think it's important to distinguish a child who's diagnosed with GERD six months and below, from the child above six months. Typically, GERD, you know, goes away in five- to sixth-month-old children where this is never really an issue. The other issue is that for all the children I send to gastroenterologists, if the parents get sick of my attempts to try to stop the kids spitting up, I have never gotten a diagnosis in two years of a child having erosive esophagitis. So I'm just curious, as to all of these children that you're seeing, what the incidence is -- if anybody knows what the actual incidence is.

CHAIRMAN TOWBIN: Dr. Baker eagerly has her hand up.

DR. BAKER: Okay. I can't answer what the incidence really is but I can tell you that we were approached to do this trial. We do between 500 and 700 endoscopies a year -- upper endoscopies in kids, about 25 percent of them are under a year -- an average thing. We had to decline this because we don't see any erosive esophagitis under a year of age. So, we had to -- we couldn't do it. But I do want to talk, as a gastroenterologist, to your talk about using these PPIs. At least in our practice, we're always stopping them. It's the primary care people that are dumping them on like crazy. So just a little aside.

DR. DRACKER: For the record, officially, I'm conservative, just so you know.

CHAIRMAN TOWBIN: Well, actually, the use data would support Dr. Baker's comment. As I looked at it, it looked as if the primary specialty using this is not even pediatrics or gastroenterology. It also suggested that the use diagnostically was not for GERD or any specific diagnosis but one of those famed NOS kinds of problems that suggests exactly what she's saying. Are there other comments before we vote -- oh yes. Thank you, Dr. Hudak.

DR. HUDAK: Yes. This is Dr. Hudak and I have to comment that as a neonatologist, I'm just very happy that with all this extrapolation, nothing was extrapolated to less than one month of age.

[laughter]

CHAIRMAN TOWBIN: Dr. Wagener.

DR. WAGENER: Yeah. I'd just make a suggestion to the FDA and that is, when you look at the package insert, the physician will go immediately to the indications and usage. That's one reason why it's up front. And when there's a scenario like this where, in a certain age group, either the approval process was different or there's unknown different kinetics, it would be nice if that was included at that point in the review -- or in the insert. So for example, under

indications and usage for the oral Nexium product, there are four bullet points that it's indicated for treatment of GER, reduction of endocet-associated h. pylori, and pathogenic -- or pathological hypersecretory conditions. There could be a fifth bullet that would say, in one-month- to-one-year olds for erosive esophagitis with hypersecretory state, something like that. So, again, this is an area that has been identified as unique. Above one year of age, we're sort of accepting the same as the adult, but since there was so much concern expressed, it would be easily solved with an additional bullet.

CHAIRMAN TOWBIN: Dr. Rosenthal, did you wish to make a comment?

DR. ROSENTHAL: No, it was made. Thanks.

CHAIRMAN TOWBIN: All right. So perhaps people are ready to say whether they concur with the request to return this to routine monitoring. Dr. Cnaan, why don't we begin with you?

DR. CNAAN: I guess I concur.

CHAIRMAN TOWBIN: Would you wish to say what your tentativeness is about?

DR. CNAAN: Yes, I have some reservations about the extrapolation in the more-than-one-month group. But it's an old reservation so I won't add anything now.

CHAIRMAN TOWBIN: Dr. Mink.

DR. MINK: I think with regard to the safety and the recommendation for routine monitoring, I concur. I share some of the concerns that have been discussed and -- including some of the labeling questions.

CHAIRMAN TOWBIN: Dr. Santana is still out so I think we're on to Dr. McGough.

DR. MCGOUGH: Again, to the safety question, I concur. I'm also concerned with -- I mean, it sounds like most of this is -- it sounds like there's a lot of off-label use by non-specialists for kids who are spitting up, which is disturbing to me. But I think to the safety question, I would concur.

DR. ROSENTHAL: I concur with the recommendations regarding continuing routine safety screening and I also agree that more attention needs to be paid to this label because I think it's -- I think it's ambiguous in a way that will promote off-label use for an indication for -- in an area where there is -- where we actually do have evidence that it's not effective. And so, I think that -- I think the current label is not just ambiguous; I actually think it's wrong [laughs], so...

DR. WHITE: I concur with Dr. Rosenthal's opinion.

DR. BAKER: This is Susan Baker. I concur with the safety issues, routine monitoring, but I really want to stress that I also concur with Dr. Rosenthal's concerns and his suggestions.

DR. HUDAK: This is Dr. Hudak. I concur with the safety monitoring recommendations and agree that something needs to be done to clarify the information on the label.

DR. CATALETTO: Mary Cataletto. I concur with the routine safety monitoring and agree with my colleagues about the indications in the labeling.

DR. LARUSSA: Phil LaRussa. I concur with the recommendation and agree with the previous comments.

DR. DRACKER: Bob Dracker. I concur with safety monitoring; however, I would submit that I think most of its use in small children is off-label as was commented upon. I also don't know how to get in -- the purple pill in a child that age anyway so...

DR. FRANCO: Israel Franco. I concur with the safety monitoring and also agree with the prior comments regarding the labeling and the off-label use.

DR. GLASIER: Charles Glasier. I agree with the safety issues and I also agree with the issues about labeling.

DR. WAGENER: Jeff Wagener. I agree with the FDA recommendations and, similar to my colleagues, encourage that under the indications section there be -- identify the under-one-year old as unique.

DR. WIEFLING: This is Dr. Wiefeling and I concur. I agree with my colleagues. I also just wanted to make sure or

clarify that it does say that the indications extrapolated deep down in Section 8. But it should be more evident to the pediatrician.

MS. CELENTO: Amy Celento. I concur with routine safety monitoring and am in agreement with the comments about the label and off-label usage as well. Thanks.

CHAIRMAN TOWBIN: So, it sounds like we have everyone concurring but there are concerns about the labeling and a request, perhaps, to look at that more closely and some concerns also about the extrapolation function. I'm not sure that there's a specific recommendation that comes from that but certainly, I think the concern about the labeling is a clear one.

DR. MURPHY: I really appreciate the discussion because one of the things the agency struggled in with 8.4 that we're now getting product studied is, as you know, for adults, if you have negative studies, it doesn't go in the label. But - - because it's required to go in the label for all the reasons you all are familiar with, we're not going to get any other studies, so it goes in 8.4 if it's negative. And so, we're now -- you're now seeing the outcome of if we have a negative study -- and we have negative studies sometimes where it -- we're not sure that it really doesn't work. It could've been a study issue, okay, versus a negative study where there is some other

issue that you're bringing up that you think needs to be highlighted. So I think that's the tension you're seeing here as to where various information gets put into the label.

CHAIRMAN TOWBIN: Dr. Yao.

DR. YAO: Yeah. I wanted to, sort of, provide some context too and I think all of the comments that the members have made are very helpful, actually, and highlight some of the difficulties we have sometimes in getting the information we really want out to prescribers within the context of the labeling and the requirements for labeling and the ability or inability to describe certain information. I can be somewhat reassuring that the Division of Gastroenterology and Inborn Errors Products is acutely aware of the issues that were brought forth from the 2010 advisory committee and have been working, I think, diligently with sponsors to try and come up with actual studies that address the questions that were raised. That is, what is really the incidence of acid-mediated erosive esophagitis in patients less than a year of age? And that largely, I -- and Dr. Korvick and Dr. Fiorentino, Dr. Wynn can add. But largely, we have now discouraged companies from performing studies in GERD in less than one year of age because it's been clear, as the advisory committee pointed out, that we don't believe that that's necessarily acid-mediated and that -- why would you be exposing these children to that risk? But

again, I hear the committee's concerns about, well, now that we've decided that we really don't want to use it, we don't want to promote it, how do we get it in there such that it's very clear that we don't really want it used. And I hear those comments loud and clear.

CHAIRMAN TOWBIN: Thank you for that. I think it's always difficult to be on that line where you're trying to inform people at the same time as you're not really in a position to dictate practice. Dr. Baker's comment about how frequently she's in the position of stopping this drug -- I think, the other thing we're seeing is how patients may be on these drugs for very long periods of time in that kind of six-to-eight-week period that is in the label is adhered to relatively infrequently. Dr. White?

DR. WHITE: Can you give us some insight into how the regulatory function of the agency is able to interact with the drug companies running the studies when they come up as a negative study since there's such an impetus not to publish negative studies?

DR. MURPHY: Are you asking -- they don't have a choice for pediatrics. Is that -- that information goes into the label. So from a regulatory point of view, we would send them a letter that basically says, "you don't get this indication, you can't market it for this," and it's going to be,

you know, put in a certain section. Now, there're negotiations that can go on, yes, but fundamentally, the final letter would be the result of any negotiations that happen to occur. But if you're trying to get at, can we put it in different places in the label? Okay -- yeah, yeah. No. There are negotiations that go on but they can -- they don't have the option to not have it in the label, I guess what I'm trying to say.

CHAIRMAN TOWBIN: Dr. Yao.

DR. YAO: And just to add on to what Dr. Murphy said. So as far as being able to label a negative study, we have that authority in pediatrics, which is not the case for adult studies and I think that's one important win that we have for children. But you have to know where that information goes and that information goes in Section 8.4. It doesn't go in clinical trials, it doesn't say it's not indicated, so you have to be a little bit savvy to understand that and that's part of the problem is that sometimes even though we are able to publish or label for a negative study, it sometimes gets a little bit buried in the information.

OPEN PUBLIC HEARING

CHAIRMAN TOWBIN: All right. Well, I think that we should move along so we stay a little bit on time. It's, I think, been a really helpful discussion and I appreciate everyone's contributions. So this is the point in our meeting where we are open for public session and there is a statement that I read as we begin this process. "Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Pediatric Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open hearing public speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any firm or any group, their products, and, if known, their direct competitors that is likely to be impacted by the topic you address in your presentation. For example, this financial information may include the payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationship. If you choose not to address this

issue of financial relationships at the beginning of your statement, it will not preclude you from speaking." And Dr. Ellenberg has some comments.

DR. ELLENBERG: Thank you. In preparing for this meeting, I did not receive any request to speak at the open public session. I did, however, receive one comment from the Sheller Law Offices. In just a minute, Dr. Towbin will read the cover letter for that information that was submitted to us. But I would like to let everybody know that this information is available out on the registration desk, it's in a three-ring binder. So after he reads the cover letter, if anybody wants to look at it, you're welcome to. The information does reference a citizen's petition that was submitted by that firm. All citizen's petitions are available to the public and so, you can go online to the docket and review that information. Now, the docket number is actually included in handwriting at the bottom of the page of the citizen's petition that you can find out on the registration table. I will let everybody know the members of the committee do have a copy of the information that I'm referring to and, at this point, I will turn it over to Dr. Towbin to read the cover letter.

CHAIRMAN TOWBIN: So, this letter was submitted by electronic mail on the 7th of March to Dr. Ellenberg.

"Dear Dr. Ellenberg. Kindly forward the attached documents listed below and this letter of explanation to the Pediatric Advisory Committees for their review and consideration regarding the Janssen atypical antipsychotic Invega, that is, paliperidone, the active metabolite of risperidone, marketed by Janssen, Johnson & Johnson as Risperdal.

The documents are citizen's petition requesting the immediate revocation of the pediatric indication for Risperdal, all generic versions of risperidone and Invega submitted by our office on July 27, 2012; public exhibits to the citizen petition, minutes, and transcript of the Pediatric Advisory Committee meeting held November 18, 2008 regarding Risperdal; citizen's petition amendment addressing deficiencies in the current Risperdal label submitted by our offices on August 27, 2012; and the FDA's interim response dated January 29, 2013 advising that the complex issues raised in the citizen petition require extensive review and analysis.

We draw your attention to the long-term safety concerns about Risperdal expressed unanimously by the Pediatric Advisory Committee on November 18, 2008," quote, "'regarding metabolic syndrome, growth, sexual maturation, and hyperprolactinaemia,'" unquote "and extrapyramidal side effects as well as the committee's request for studies on the," quote

"`long-term effects in the pediatric population of this class of products,'" close quotes.

And they quote Exhibit B minutes, Page 6. "To our knowledge, only a single long-term study of Risperdal was initiated in response to address this long-term safety effects on growth, sexual maturation, and hyperprolactinaemia. See clinicaltrials.gov." Quote, "'A study to evaluate the safety and the effects of risperidone compared with other atypical antipsychotic drugs on the growth and sexual maturation in children, with the ID number NCT01050582.'" The posted results of this interventional study comparing children on Risperdal with an N of 133, with those on other atypical antipsychotics with an N of 51, for a minimum of six months are inconclusive. As the study was, admittedly, imbalanced in the number of subjects in each arm and was terminated early. Additionally, the number of retrospective reported prolactin-related side effects was listed as seven in the Risperdal group and three in the," quote, "'other group but does not disclose either what these events were or the incidence of each. The results also do not address the longer-term safety effects of children on Risperdal, of major concern, because as we understand it, general clinical practice is to prescribe Risperdal to these children for years, rather than months. Our concern is that the safety issues raised by the prior Pediatric Advisory Committee

regarding Risperdal's use in children were not answered. Additionally, we are not aware of any long-term safety studies or trials answering these same questions regarding pediatric use of Invega, a more potent form of Risperdal. This is despite the safety review of Invega dated March 8, 2011, found among the briefing materials for your meeting; which includes long-term data, only so far as six months, per the footnotes of the adverse event table cited within. Consequently, we are concerned that the current Pediatric Advisory Committee would be taking premature action in considering the use of Invega in children," open parentheses "under the age of 12 years," close parentheses, "with schizophrenia. This is particularly so because, as we understand it, the diagnosis of schizophrenia in preadolescents is not a settled or standard practice. In our representation of boys who use Risperdal and developed gynecomastia, we have uncovered information, which we believe should be made available to the Pediatric Advisory Committee, but which we are not at liberty to share because of the confidentiality/protection orders. We submit that the Food and Drug Administration require this information to be made available to the Pediatric Advisory Committee so that the Committee can fairly and fully evaluate the safety data on Risperdal and --" I'm sorry, "Risperdal and Invega in children.

Failure to do so is a serious and egregious error, leaving the Pediatric Advisory Committee to act in the dark.

Sincerely, Stephen A. Sheller, Esquire and Pricilla M. Brandon, Esquire."

That concludes the open public hearing -- oh, Dr. Drecker, do you have a --

DR. DRACKER: I'm not a psychiatrist; I don't play a psychiatrist at all, but I have to tell you, the number of children that benefit from Risperdal, even on my own practice, is tremendous. Especially children with Asperger's syndrome and others. Studies have shown its usefulness for certain populations of children, number one. Number two, I have -- and my daughter's an attorney, so it's nothing against a law firm sending a letter, but this sounds like in preparation of a class action law suit to me. Maybe that's an inappropriate comment, but -- I have no problem with, maybe, increase surveillance or relook at the data and safety and recommendations, but in children, this has been a very valuable medication, especially for children who are aggressive and are very difficult to control. And most physicians, I think, are very diligent as far as watching adverse side effects of long-term use.

CHAIRMAN TOWBIN: All right. So I think this brings us to a break. We could reconvene, I guess, 10 of 1:00? 10 of 1:00. See you back.

DR. ELLENBERG: Just a reminder on a couple things. The hotel does have a buffet downstairs that you can go; I believe the cost is approximately \$12. There are also other restaurants around the area. I also would remind you that you are not to speak and talk or discuss these matters that you've discussed this morning or any that you may discuss this afternoon with any of your colleagues or anybody in the public once we're at lunch. Thank you very much; we'll see you at about 10 until 1:00.

INOMAX (NITRIC OXIDE)

CHAIRMAN TOWBIN: All right, everyone, I think we're going to start up again. Before we hear Dr. Radden's presentation of INOmax. I believe -- Dr. Cope, were you going to make a statement? And then I just wanted to point out to everyone that Dr. Cataletto and Dr. Cnaan are away from the table for this discussion. So, Dr. Cope.

DR. COPE: Yeah, I just wanted to make a comment before we get started. Can you hear me? Okay, I will speak up. Before you get started on the INOmax, I just wanted to point out to you, let you know that there was a recent labeling change. In the slide presentation, things that'll be mentioned about the labeling may not be the most updated, but it will correspond with the labeling that you received in your background materials. However, we have furnished you with the latest updated label in a blue folder that sits in front of you on the table. If you open it up, there'll be two documents. One is the new label that just came out shortly ago. And the other is a long letter that basically says what the changes were made for this new labeling. So we just wanted to be sure. We never want to go to a meeting and you not have the very latest label, so...

CHAIRMAN TOWBIN: Thank you very much, Dr. Cope. So we're going to hear from Dr. Radden. Welcome back, Dr. Radden. It's always a pleasure. Dr. Radden is a family practice

physician who received her medical degree from the Uniform Services University of the Health Sciences and completed internship and residency training at Malcolm Grow Medical Center on Andrews Air Force Base, with the National Capitol Consortium. She recently separated from the U.S. Air Force after 14 years of service and joined the United States Public Health Service. Prior to joining the Food and Drug Administration, she practiced at Dover Air Force Base, where she served as the medical director of the Family Practice Clinic in addition to the deputy chief of the medical staff. Dr. Radden.

DR. RADDEN: Good afternoon, everybody. Welcome back from lunch. So today I'm going to discuss the safety review for INOmax, or nitric oxide. I will be following this familiar outline; however, in the adverse event review, I will discuss cases identified from searches in two different databases: AERS and MAUDE, which will be described further later.

So INOmax is an inhalation gas and vasodilator, which in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term- and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. INOmax was originally approved in December of 1999. Due to its orphan designation, no post-marketing studies were required under PREA. However, a study was performed under BPCA in which INOmax was studied for the

prevention of bronchial pulmonary dysplasia, or BPD, in preterm neonates. Efficacy was not established and these findings were included in the labeling in December 2010, prompting this safety review.

I want to provide some background on the devices used to administer INOmax. There are three delivery systems that are used in conjunction with a ventilator or other breathing gas administration system: the INOmax DSIR, the INOmax DS, and the INOvent, which are shown here.

Two pediatric studies were conducted that showed efficacy of INOmax for pulmonary hypertension and formed the basis for the initial approval of INOmax. The first was the NINOS Study, which also showed a lack of additional benefit at higher doses of nitric oxide in infants who had not response to the approved dose of 20 ppm or control. The primary endpoint of an improvement in death or need for extracorporeal membrane oxygenation or ECMO, however, was achieved. The second study was the synergy study, in which the need for ECMO was evaluated in neonates given INOmax for pulmonary hypertension in hypoxic respiratory failure. Although mortality was similar, significantly fewer neonates given INOmax required ECMO. As stated previously, the study this safety review -- the study prompting this safety review evaluated the safety and efficacy of INOmax for the prevention of BPD in neonates requiring

respiratory support. Efficacy was not established in three multi-centered, double-blind placebo control clinical trials, including over 2,000 neonates treated for seven to 24 days. The results of this study was summarized in Section 8.4, Pediatric Use, and 14.3 in clinical trials.

Now we will discuss the relevant INOmax safety labeling, focusing on conditions which you will see again in the review. Contraindications and warnings and precautions are listed here. I'd like to call your attention to the warning for worsening oxygenation or hypoxemia with abrupt discontinuation as this will appear later, as I discuss the adverse events. Mortality and duration of hospitalization were similar in the NINOS and CINRGI trials. Additionally, six-month follow-up of patients revealed no evidence of increased re-hospitalization, special medical services, pulmonary disease, or neurological sequelae with use of INOmax in clinical trials. Several adverse reactions were noted in at least 5 percent of patients in the CINRGI study, which are seen here. However, there was no statistical difference between the INOmax and placebo groups. Pay particular attention to the reactions of withdrawal, hyperglycemia, sepsis, and infection. I also call your attention to dose errors, hypoxemia, and pulmonary edema noted in post-marketing experience.

Now we will turn our attention to the use of INOmax. This table shows the number of hospital visits in patients by patient age who were billed for INOmax from U.S., non-federal in-patient hospital setting. Over the cumulative time period of November 2010 through May 2012, approximately 33,000 hospital visits and 32,000 patients were billed for INOmax. The majority of patients were age 17 years and older. Patients zero to 1 years old accounted for around 37 percent of total patients and approximately 6 percent of total patients were 2 to 16. Neonatal use is reported by location of use since age cannot be categorized any further. Among patients zero to 1 years old, approximately 58 percent of the patients received INOmax in the NICU. Among patients 2 to 16 years old, approximately 51 percent of them received INOmax in the PICU. Among patients 17 years and older, approximately 75 percent of these patients received INOmax in the ICU.

Now let's look at the pediatric focus adverse events from the AERS database search. Of the 39 pediatric adverse events reported since the pediatric exclusivity date, all were deemed serious and included 18 deaths. Further examination of the no-value reports were billed one serious pediatric report and three pediatric death reports.

I will now walk you through the case selection. Recall that we began with 39 total pediatric reports, including

18 deaths, with 1 non-fatal serious report, and three fatal reports found in the null values for a total of 43 pediatric reports, including 21 deaths. There were 6 duplicated reports, 3 of which involved deaths. This leaves us with 37 unduplicated pediatric reports, including 18 deaths. Two reports were excluded as they were erroneously reported as serious.

Therefore, 35 serious pediatric cases, including 18 deaths, remain to comprise the case selection. Available data shows that the majority of serious pediatric cases involve neonates with gestational ages between 23 and 27 weeks, and postnatal ages at initiation of INOmax from birth to one month. Keep in mind that INOmax is approved for neonates with a gestational age greater than 34 weeks as you listen to these reports. I will first focus on the 18 fatal reports, which can be classified as shown here. You will notice that 13 of the 18 fatal reports involve off-label use either due to age of the patient or indication for treatment. Also, please keep in mind that the vulnerable populations that are described in these reports and how their concomitant medical issues may have contributed to their deaths. Given the device issues in the AERS search, the safety review was augmented with cases from a search of the MAUDE device database, which I will discuss later. So the following reports initially describe those found in the AERS

search and conclude with the device-related adverse events reported from the MAUDE search. Keep that in mind.

Unlabeled adverse events are underlined. I will now review the six cardiovascular fatal reports. The first report involved a 23-week gestational age neonate with multiple medical issues associated with prematurity, who was started on nitric oxide, or NO, via the INOmax DS device for pulmonary hypertension. The neonate developed brada cardia and hypoxia and died after multiple resuscitation attempts. Note that the neonate was concomitantly administered fentanyl, which is labeled for brada cardia. Also, INOmax is labeled for hypoxia. The next report is of a male neonate administered INOmax for hypoxic respiratory failure associated with pulmonary hypertension. He developed hypotension and brada cardia, resulting in cardiac arrest. Note that the neonate was also given midazolam, which is labeled for brada cardia. In the next report, a full-term male neonate with a history of meconium aspiration was started on NO after developing acidosis and hypoxia. He died of cardiovascular collapse, which had started prior to the initiation of INOmax. The next three cases describe literature reports of patients with pulmonary hypertension ranging in age from four to 15 years old, who were undergoing surgical procedures under anesthesia. You can see the details here. In the first two cases, the patients were

being ventilated with NO for their respective procedures and subsequently developed brada cardia and arrhythmias followed by death. Both patients were administered anesthetic agents that are labeled for arrhythmias and/or brada cardia. And in the first case, the patient's procedure of cardiac catheterization is associated with arrhythmias. In the last report, the patient developed acute pulmonary hypertension in association with her procedure, which was treated with oxygen and NO. However, she suffered cardiac arrest and died despite resuscitation efforts.

The following five cases describe fatal reports in which an INOmax delivery device was involved. Although a device failure was reported as the primary adverse event in each case, the issues occurred in the context of the patient's primary disease and in none of the cases does the agency believe the device failure was the primary cause of death. The first report is of a one-day-old, full-term male neonate with poor prognosis of survival due to multiple medical issues and congenital anomalies, who was started on NO via INOvent DS for hypoxia. He was initially maintaining his oxygen saturation when the device alarmed electronic shutdown and oxygen saturation fail. Despite manual ventilation with an INOBlender and switching to a working unit, oxygenation did not improve and the patient suffered cardiac arrest after multiple resuscitation attempts. Note that this case will be referenced later as it was also reported in

the MAUDE database. The next report is of a 24-week gestational age, critically ill female neonate who was started on NO for persistent pulmonary hypertension of the newborn, or PPHN. After initial response, the device alarmed and shut down and oxygen saturation failed. NO was discontinued because the patient did not respond to ventilation with an INOBlender and no other device was available. The patient died of cardiac arrest. In the next case, a 33-week gestational age female neonate was started on NO via INOmax DS for PPHN. Multiple device issues occurred and the neonate was manually ventilated with an INOBlender after each device failure. She also developed a GI bleed and died after life support was withdrawn. Note that labeling indicates that in the NINOS Study, the placebo in NO groups were similar with respect to the incidents and severity of GI hemorrhage. The next fatal device report involves a critically ill neonate started on NO via INOmax DSIR for pulmonary hypertension. The device alarmed that a cylinder was not detected. The cylinder was replaced despite no apparent malfunction. However, life support was later withdrawn and the patient died. In the final device-related report, a full-term female neonate with meconium aspiration and PPHN was intubated with fixed and dilated pupils and started on NO via INOmax DS. The device alarmed due to a closed NO tank caused by human error. The patient died after supportive care was withdrawn.

Note that in these critically ill patients, device failure did not appear to be associated with any of the decisions to withdraw life support.

You will hear more about the device reports identified in the MAUDE search shortly, but now I'll continue with the review of the remaining cases found in the AERS search. The only fatal respiratory report is of a 27-week gestational age female that was switched from a conventional ventilator to a high-frequency oscillatory ventilator due to hypoxia and acidosis. She developed a bowel perforation and underwent surgery. NO was started but her condition did not improve and she died of cardiopulmonary arrest after life support was withdrawn. There were four fatal miscellaneous reports. The first involved a 27-week gestational age female with oligohydramnios, who was placed on a high-frequency oscillatory ventilator and started on NO for respiratory distress syndrome. She developed an intraventricular hemorrhage and died. The next report is of a 34-week gestational age critically ill female with hydrops fetalis and pulmonary fusions who was ventilated and started on NO but died after life support was withdrawn due to her underlying medical conditions. Note that labeling indicates that in the NINOS Study, the placebo and NO groups were also similar with respect to incidents and severity of intraventricular hemorrhage. In the next report, a 36-week

gestational age male with respiratory distress transposition of the great arteries and pulmonary hypertension was started on NO without effect and received a balloon atrial septostomy. He developed endocarditis and died despite resuscitative efforts. The last case is a literature report of a 7-year-old female with exertional cyanosis and pulmonary arterial hypertension, who had normal left-sided heart function but developed pulmonary edema after treatment with NO and sildenafil. Despite treatment with doxycycline and interferon alpha 2a, she died, and a lung biopsy confirmed preexisting pulmonary capillary *hemangiomatosis*. Her death appears to be associated with her underlying condition. However, related INOmax labeling describes pulmonary edema in the adverse reaction section. The final two fatal reports had insufficient information to assess causality. In the first, a 13-year-old female with pneumonia was started on NO for ventilator profusion mismatch and developed fatal malignant hyperthermia and insulin resistance. Lung abscesses were noted on autopsy. In the second report, a premature neonate was started on NO for unknown reasons and died the same day. Recall that INOmax labeling includes hyperglycemia and infection in adverse reactions.

Now we will turn our attention to the serious nonfatal adverse events, of which there were 17, and are classified as seen here, with device issues comprising the largest proportion.

Keep in mind that these reports on device issues do not necessarily include device reports submitted to the MAUDE database -- device database -- which will be discussed later in the review. There were several reports of device issues, four of them occurring in preterm infants. Three of the reports involve device misuse, resulting in oxygen desaturation due to a mucus plug, alteration of the device circuit, and a plugged endotracheal tube. Although this last case was classified as a device misuse, the device did not prompt the desaturation. Three of the reports involved the device failure with desaturation, and you can see the details here. I would just like to point out that the INOmax labeling includes hypoxemia, withdrawal, and dose errors. There were three cardiac reports, all involving preterm neonates requiring mechanical ventilation, who were enrolled in a clinical trial for NO for BPD prevention. All the patients had a preexisting patent ductus arteriosus, or PDA, that was treated with indomethacin, but reopened or worsened within three days after NO was initiated. They recovered following surgical ligation. These cases are confounded by the patients' underlying prematurity and preexisting PDAs. Three reports involve preterm neonates with sepsis, that is suspected -- that it is suspected was present at birth. In one report, the patient also had necrotizing enterocolitis, and sepsis occurred 12 days after NO was

discontinued. In the other two, sepsis occurred during NO administration. Note that INOmax labeling includes sepsis and infections.

There were two nonfatal respiratory reports. In the first, a -- sorry. There were two nonfatal respiratory reports. In the first, a premature neonate with a patent foramen ovale had a desaturation after NO was adjusted. Saturation improved after CPAP was repositioned and NO was continued. In the second report, a premature neonate with pulmonary hypertension and heart problems was started on NO with initial improvement but subsequent decrease in oxygen saturation. The patient recovered after NO was discontinued but NO was restarted with no further desaturations after the patient required chest compressions and manual ventilation. A pneumothorax was noted on x-ray. Note that INOmax is labeled for hypoxemia. Additionally, pneumothorax is associated with intubation and mechanical ventilation in preterm infants. One dermatologic report involved an 8-year-old female on Methylphenidate for ADHD who developed an urticarial rash and facial swelling 2.5 hours after receiving propofol for anesthesia induction and NO oxygen and Sevoflurane for anesthesia maintenance. She also received premedication with ibuprofen and acetaminophen. She recovered after all the medications were withdrawn. Note that propofol, Methylphenidate, and ibuprofen are labeled for anaphylactic

reactions. Also, nitric oxide used in this case may have been erroneously reported for nitrous oxide use, since no indication for nitric oxide was noted. The single hematological report of an 18-month-old male enrolled in a clinical trial for -- of NO for adjunctive treatment of cerebral malaria who developed worsening anemia. NO was discontinued and a blood transfusion was given, resulting in stabilization of hemoglobin levels. Of note, malaria is a well-known caused of periodic and sudden decreases in red cell mass and anemia.

Finally, we will discuss the pediatric adverse events identified in a search of the MAUDE database. After a review of adverse events in the AERS database, it was discovered that five deaths and seven serious, nonfatal pediatric AEs involved the device that administered INOmax. Therefore, an additional review was conducted in the manufacturer and user facility device experience database -- the MAUDE database to further investigate any pattern of adverse events involving INOmax delivery systems. A search was conducted from November 2010 through October 2012 for reports involving all three INOmax delivery systems. One hundred and eighty total medical device reports, or MDRs, were found. Note that the age was only reported in 47 of the 180 MDRs, so the information was limited in the classification of the pediatric cases. One hundred and fifty-one MDRs involved adults or reported no age. Twenty-nine pediatric MDRs were

identified, including one death, nine injury reports, 13 malfunction reports, and six other reports. A recall occurred for the INOmax DS system in August of 2010 due to the potential for the pressure switch to fail and interrupt or delay the administration of INOmax. Most of the identified MDRs occurred during the time of this recall, and a number of reports decreased following the recall. The one fatal report identified in the MAUDE search was previously described in the device issue's fatal adverse events from the AERS search on Slide 25. You may have recalled this neonate had multiple medical issues and congenital anomalies and experience hypoxia following device shutdown and had a cardiopulmonary arrest. The nonfatal injury events involved pediatric patients up to 13 years of age and included device failures, disconnections, improper gas flow or output, misassembly, and no display. The majority of reports involved the INOmax DS. The nonfatal malfunction events involved pediatric patients up to 26 months of age and included the various issues seen here. Again, the majority of reports involved the INOmax DS. Finally, the six events classified as "other" involved the very issues noted on the slide and INOmax DS was, again, the system involved in the majority of reports.

Oh, I want to say one other thing. Sorry. Aside from the single fatal report, the other reports involved desaturations or delay of care that was generally temporary and

resolved without contributing to any long-term effects. No concerning pattern was noted in the 29 pediatric reports. This concludes the pediatric focus safety review. As a result of the studies conducted under BPCA, labeling reflects the lack of efficacy of INOmax for bronchopulmonary dysplasia. The safety review, including both the AERS and MAUDE searches identified no new signals, and the FDA recommends continuing routine monitoring. Does the committee concur? We would also like the committee's input on whether device issues should be reported to the current FAERS, the MAUDE, or both databases. And I would like to acknowledge the assistance of the people in this slide. Thank you.

CHAIRMAN TOWBIN: Thank you very much, Dr. Radden. So if we could begin with discussion of, I think, either one of these questions, and of course we'll come to the vote when we're ready. Dr. Yao?

DR. YAO: Sorry, just for the committee members, I just want to announce that Dr. Murphy had to leave with a personal emergency and we have Dr. Skip Nelson here, who is from the Office of Pediatric Therapeutics, and senior pediatric ethicist for -- in her place.

CHAIRMAN TOWBIN: I'm delighted to see Dr. Nelson join us.

DR. NELSON: My pleasure.

DR. MINK: Could you just -- yeah, could you just redefine the FAERS versus the MAUDE database, what their intentions are and what would go where and what should we base our decision on?

CHAIRMAN TOWBIN: Dr. Hausman.

DR. HAUSMAN: Ethan Hausman. I'll address the FAERS database first and a little bit of MAUDE. And then I think we have some device folks here, they may want to add in on that. The FAERS database is for drugs and biologics. And when a practitioner suspects that an adverse event occurs in a patient that they treat with drug X, they can go through the web portal and make an event report. The MAUDE database is the device correlate where people can submit device failures into an adverse event system. For example, if you're -- if you have a newborn screening device, and you have a failure of one of your chemical controls so everything looks positive, that would be a device failure. And you would submit that into CDRH's adverse event system.

CHAIRMAN TOWBIN: Dr. White.

DR. WHITE: Michael White. Ethan, can you tell us, is there an advantage to -- or disadvantage of having them reported to both?

MS. CILLIE: Good afternoon. My name is Tam Cillie and I am from the FDA Office of Surveillance and Biometrics. I

would just like to add a comment regarding the MAUDE database. The MAUDE database collects information from user facilities, which will be the end users, and also from the manufacturers of the INOmax delivery systems. So with that type of information, we're able to collect post-market data regarding any device failures or malfunctions of the INOmax delivery systems.

CHAIRMAN TOWBIN: So would you prefer that they be reported to both, or individually? Or just to one?

MS. CILLIE: The advantage of having the reports entered into both would be that we could simultaneously, from the device side and the drug side, sort of, get a bigger picture of what's going on with the system entirely. I think there is limitation when we are separated by reports going into the MAUDE database versus the VAERS database.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: Is there a manufacturer requirement for a standardized SOP to be in place before the device is used at institutions?

DR. HUDAK: This is Dr. Hudak. There's not.

DR. SANTANA: I mean, most institutions have the device go -- This is Victor Santana. Most institutions that use devices do it two ways. They usually have their bioengineering department review the device and get a clearance before it's released to the clinical area. And then nursing or respiratory

therapy, or wherever the service is, then will develop an operating procedure of how that device is to be used. That's fairly standard from my experience in my hospital, N of one [spelled phonetically].

DR. DRACKER: It would just seem to me, like you would see -- let's say with an ECMO device or others, that the manufacturer should have some responsibility to show them what type of SOP should be in place at the institution to make sure that there's not a mistake with the mechanical aspect of the administration.

CHAIRMAN TOWBIN: Dr. Hudak.

DR. HUDAK: This is Dr. Hudak. So I'll answer that. I'm sorry, I thought I -- I thought you asked whether or not there was a standard operating procedure for which patients it was used. There's not. But with respect to this, every institution has its own biomedical engineer processing for sure, and in terms of actually how the device is set up, at least in our institution and others I've been working with, company representatives have come in and trained the respiratory therapists and other involved personnel as to how to set the device up and how to use it safely. So I think it may not be completely written down in stone but it's a pretty consistent procedure.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: Yeah, I guess my only comment about double reporting is that when you ask people to report the same thing twice, there might be a -- let's say, a chance that they're not going to report it at all. So if there's a way of choosing the one that's most appropriate and then having that populate the other, if that would help, I would do that. But to ask them to fill out two different sets of reports, I think is -- gets to be onerous on people.

CHAIRMAN TOWBIN: Dr. Santana.

DR. SANTANA: So what struck me in the presentation is that there's not a lot of overlap in the current reports that you were able to find, that there were very few cases that it was reported in both. So what tells me is that there are a group of individuals that think that it's a drug and they're more familiar with the now FAERS system, you know, so they report it as a drug. And then there's other individuals that think, "Well, maybe this is related to the device," and they report it through that mechanism. So what that tells me is that you really need both if you really want to have a denominator that really tells you how big the problem is because there's not -- you know, people are thinking of reporting based on their own way of that they think they should report, and there's not a lot of overlaps, and you could always identify the overlap like you did today. So it seems to me like a more robust way is to allow

people to report through both systems and then somehow you bring it together when you analyze the issue.

CHAIRMAN TOWBIN: Dr. White.

DR. WHITE: Michael White. I would like to go along with what you're saying. I think that device failures are most likely to show up with the respiratory therapists or the nurses that are running the devices. And they're going to follow their reporting procedures and it may not be something that the physician would be aware of even, whereas physicians and medical staff are more likely to be reporting through the FAERS system. And I think what I was getting at when I asked you the question was is there a disadvantage to dividing -- yeah, I think probably the best way to do this is report to both, or allow reporting in both and have some way of identifying, you know, is there a duplicate report? Which you probably can figure out pretty easily -- I don't know how the device format is compared to the medical format for the FAERS, but, you know, maybe you just need to change the format so that you can identify duplicate entries or concurrent entries. I mean, there may be device failure and medical therapy failure at the same time, potentially.

DR. RADDEN: I just want to make a comment that I did review the one report that was duplicated. It did appear that a

respiratory therapist submitted the same report just to both databases.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: From your perspective, were most failures or problems with therapy device-related? Could you tell?

DR. RADDEN: I'm sorry, say that --

DR. DRACKER: Were most issues device-related?

DR. RADDEN: Most issues were just the device reports or --

DR. DRACKER: Well, no. All the reports, were most of them related to device problems? Could you tell?

DR. RADDEN: I would say --

CHAIRMAN TOWBIN: Dr. Hausman.

DR. HAUSMAN: Ethan Hausman. From the reports that came through FAERS -- I'll talk about FAERS. Most of the infants who died, died from complications of their diseases and the several device failures that we saw, mucus plugging, for example, can set off an alarm code that reads as a device failure but it's intrinsically part of the path of physiology of the disease. There was a reboot of a system for an undetermined reason because the level of the code error that set that off was not, in fact, reported, so there's no way to tell. And that's what we found in FAERS when we looked at them. It didn't appear

to be that the device failures were proximately related to the adverse event report, whether it was a morbid one or not. And in fact, out of all the FAERS reports reporting death, I believe all of them appeared -- in the neonates, anyway, all of them appeared to be related to complications of disease.

DR. DRACKER: However, mucus plugging could theoretically be, perhaps, lack of surveillance of the device delivering the therapy, is that correct?

DR. HAUSMAN: I would say I think so. If I interpret your question --

DR. DRACKER: I'm trying to separate out what -- do you really feel that the adverse events that are being reported to you are specific to the medication or specific to the deliver and the path of physiology of what's going on? Because nitric oxide innately is fairly inert --

DR. HAUSMAN: Yes.

DR. DRACKER: -- to be honest with you. So in all likelihood, some -- it's not likely the medication itself is causing an adverse event. I'm just -- I know, I'm just saying. Historically, nitric oxide, I think -- and maybe I'm speaking out of turn -- is fairly benign. There are some vaso-reactive effects of it. I understand that. I'm just trying to get to the essence of what the problem is here. And I'm not trying to belabor the fact of this SOP issue. But when you look at other

devices, whether it's the daVinci device or other things, you can't breathe crooked. Everything that has to be done has to be done in a proper way; not just set up, but monitoring the use of the device while it's going on. That's all I'm saying.

DR. HAUSMAN: I will -- I'll address the second part of your comment because I think that's the one that's come up a couple times. As far as SOPs for how devices are used, devices like drugs come with labeling instructions for use. It's their correlate to indications for use for the drug. The device labels are supposed to have enough information to be able to use the device in the appropriate setting for the appropriate population. Beyond that, there are SOPs like when you have to do apheresis circuit, although I understand even though they're devices, they may be covered by Cyberex [spelled phonetically], some of the apheresis devices. Beyond that, hospitals develop their own training processes to -- the more complicated the device is, the more well-developed those training processes are.

CHAIRMAN TOWBIN: Dr. LaRussa, did you have another comment you wanted to make?

DR. LARUSSA: Sure. Maybe I misunderstood the original comment. Were you referring that you wanted one individual to report to both systems or you wanted both systems available for different individuals to report to? Does that make sense?

MS. CILLIE: Yes. I was referring to the fact that the end user -- because the end user is the first person to experience any device problem or potential drug interaction problem, that the end user report to both databases or be able to report to both databases, in a least burdensome way.

DR. LARUSSA: Yeah, I guess what I'm thinking is that if you're talking about a single individual like a respiratory therapist, you know, as was mentioned before, they're likely to think of it as a device and maybe other providers are likely to think of it as a med, and rather than having them -- having a requirement for both of them, for one person to report to both systems, maybe allow the people to report to the system that makes the most sense to them, and then combine them.

CHAIRMAN TOWBIN: Yes, Dr. Hausman.

DR. HAUSMAN: Yeah, I was just kindly handed an excerpt from the new label and regards to training, I believe it's in Section 9 of the label, it reads, "Training and administration. The user of INOmax and nitric oxide delivery systems must complete a comprehensive training program for healthcare professionals provided by the delivery system and drug manufacturers." The second sentence says, "Health professional staff that administers nitric oxide therapy have access to supplier-provided 24-hour, 365-day per year technical

support on the delivery and administration of INOmax." And then it gives a telephone number. This is Section 2.2 of the label.

CHAIRMAN TOWBIN: Yes, Dr. Wiefeling.

DR. WIEFLING: I just wanted to comment on that also. This is Bridgette Wiefeling. They also have in there that you have to have backup nitrous. They -- a generator and backup nitrous in the label.

CHAIRMAN TOWBIN: DR. WAGENER.

DR. WAGENER: Jeff Wagener. So I think we've beaten this one to death, and I wanted to pull up the question, "Does the safety review identify a new signals?" Can you go to Slide 35, please? This is the cardiac one and reports three cases. I guess I've got a different numbered slide than you. Go forward. Other way.

DR. RADDEN: The other way?

DR. WAGENER: Back. Keep going the way you're going. There you go.

DR. RADDEN: Which one?

DR. WAGENER: It's not important. There -- you -- there's a cardiac -- three events which are chemically indomethacin closed PDAs that were then opened coincident with the administration of inhaled nitric oxide. I don't see anywhere that that is reported in the package insert. Is that something that should be included? In other words, is this seen

as a potential risk? I can understand physiologically why it would be, and, therefore, if we're seeing it in three cases, shouldn't that be considered?

DR. HUDAK: This is Dr. Hudak. So the issue with ducts and their being opened or closed is a very dynamic situation. In small babies in the [unintelligible] closure but ducts are -- they will be open in a fair percent of babies after that time. The other point to note is that in the three large trials of preterm babies, the nitric oxide, there was not a signal that there was an increased incidence of PDA from those data.

CHAIRMAN TOWBIN: Dr. Wagener, did you want to say something in response to that?

DR. WAGENER: So that -- I mean, I recognize those numbers, but that's the whole reason for FAERS, is to see whether or not something that wasn't identified in the randomized control trials might be identified in clinical usage. And it -- again, of all the -- all of the side effects, other than the machine problems, this is the highest frequency of anything that showed up, and it seems like it might be something of concern. Or at least a warning to the people who are using the drug.

DR. WITZMANN: Hi, this is Kim Witzmann. I'm from the Division of Pulmonary Allergy and Rheumatology Products. With

regard to the BPD studies, which have been referred to, Section 14.3 of the label, which is the section that talks about ineffective and prevention for bronchopulmonary dysplasia, which included the databases from those three studies, actually says that there were no meaningful difference between treatment groups with regard to death and that hemoglobin levels, adverse events commonly observed in premature infants, including intraventricular hemorrhage patent ductus arteriosus, pulmonary hemorrhage, and retinopathy prematurity. So that was addressed and it is captured within the label to say that there wasn't a difference between the groups. I think what you're seeing is just the period of time that this reporting system covers. Those patients happen to also be picked up in the FAERS system.

CHAIRMAN TOWBIN: Dr. White.

DR. WHITE: Michael White. Actually, I wanted to focus on your labeling because one of the things you wanted to do is label that there is no efficacy in BPD. And I'm going to get Dr. Hudak to help here. It seems to me that the studies that were done were looking at very gross measures of efficacy for BPD, for periventricular hemorrhage and such. I mean, head ultrasound is not the most sensitive study one could do using oxygen at 36 weeks. We still haven't done good control studies of oxygen in neonatology, which is a drug that's long been off label and off patent. And so using that as your measure of

efficacy because someone chooses to use it in a 36-week infant because it might be helpful or not seems like a very poor measure of efficacy for BPD using the nitric. And I would caution against warning or publishing data that uses such gross measures of efficacy to say that it's not an efficacious drug. Maybe I'm wrong on that. That's why I would like a comment.

DR. HUDAK: Well, I think in neonatology, there's a lot of emotion and as much emotion and opinions about nitric oxide in premies is about any other subject -- oxygen too. But the point of the statement that said that it's not been shown to be effective, the data are the data. There -- I mean, there were basically three large studies. They studied three different populations of babies with three different hypotheses, three different treatment protocols. And there was only one study that credibly was structured to test the hypothesis whether nitric oxide was effective in reducing the incidence of BPD or death at 36 weeks. And that study did show it to be effective, so I think there's a lot of -- I understand the agency's position that looking at all of the data together and doing your analysis that there's not a consistent effect. But I think the question -- still begs a question. With respect to the measures of BPD, unfortunately, you know, the most sophisticated measure we have is do an oxygen challenge test at 36 weeks. And that is the best measure we have of BPD, and that

is what at least two of those studies, I think, were able to report on.

CHAIRMAN TOWBIN: So I'd like to begin to gather the comments a little and move us toward the vote. Dr. Wagener, you wanted to have another comment here?

DR. WAGENER: I'm going to bring this back to the FDA because I totally disagree with the response that it's mentioned in here. If you read what you just read, it mentioned there was no difference in *methemoglobinemia*, and yet we put under warnings and precautions *methemoglobinemia*. So the fact that it wasn't seen in three trials doesn't mean that it shouldn't be considered a potential serious adverse event. If, indeed, nitric oxide increases the risk of reopening a PDA, that should be in the package labeling, and it should be a warning to the physician. Given the fact that they frequently do reopen, I agree with that. I have no question there. But if this is a risk, it ought to be identified.

CHAIRMAN TOWBIN: Dr. Hudak.

DR. HUDAK: So -- I think the -- I mean, one has to look at all the information in its totality. So clearly there's good rationale for thinking that giving an agent that lowers pulmonary vascular resistance is going to lead to a tendency to reopen ductus because, after all, it's the pressure gradient between -- or the resistance gradient between the two circuits

is sort of -- is functional much flows goes to that duct. So it is rational to think that. On the other hand we have, you know, over a thousand babies in these studies, and babies who are control babies versus babies who are treated babies. And there was no signal in any one of those studies nor in the three studies put together, that there was an increased risk of PDA in the nitric oxide-treated group. And as I said, PDAs open, you know, after treatment, you know, in a significant fraction of cases, and in my mind, people reporting three instances where it reopens in a susceptible population is not enough information to say that this needs to be a warning on the label.

CHAIRMAN TOWBIN: So I think what I would like to do is to move us to vote on the question itself. And I think that maybe the best way to do this would be -- since the second question is really one that allows people to offer their opinions, I think we should at least address the concurrence with returning this to routine monitoring first, and then we'll go around again and people can state what they would like to advise. I guess what I'm hearing from our discussion about that -- I'll make some comment about that before we go around and people can state their comments. So if we can bring the question up one more time. I think what's before us is whether we think that returning this to routine monitoring is the proper step. So I think, Ms. Celento, we'll start with you.

MS. CELENTO: Amy Celento. I concur.

DR. WIEFLING: Bridgette Wiefling. I concur.

DR. WAGENER: Jeff Wagener. I disagree. I think that we need more information as far as a potential risk factor.

DR. GLASIER: Charles Glasier. I concur.

DR. FRANCO: Israel Franco. I concur.

DR. DRACKER: Bob Dracker. I concur.

DR. LARUSSA: Phil LaRussa. I concur.

DR. HUDAK: Mark Hudak. I concur, with the additional thought that given that the vast majority of use of this product is off label, it would be intriguing in subsequent reports of the routine monitoring to look at trends in use by age group. I'm very curious to, sort of, see what happens.

DR. BAKER: Susan Baker. I concur.

DR. WHITE: Michael White. I concur, and I think you should leave the reporting open to FAERS or MAUDE for the devices and the drug effects.

DR. ROSENTHAL: Geoff Rosenthal. I also concur.

DR. MCGOUGH: Jim McGough. I concur.

DR. SANTANA: Before I vote, I just want a point of verification. Are there any other commitments for additional post-marketing studies with this device and this agent? Are there any outstanding post-marketing studies that have not been brought in?

CHAIRMAN TOWBIN: If someone could just say yes or no, that would help.

DR. WITZMANN: Kim Witzmann from the FDA. I -- with regard to the BPD indication, there have been no post-marketing commitments or requirements that are currently available, and I am not sure with regard to the cardiac indication for pulmonary hypertension.

DR. SANTANA: Thank you for clarifying that. This is Victor Santana. I concur.

DR. REED: Michael Reed. I concur.

DR. MINK: Jon Mink. I concur.

CHAIRMAN TOWBIN: All right. And so, now I think we can begin to address the second question, although I think one of us has already spoken about it. But I think that it would be helpful if people could say what they think about the reporting system. What I heard as sort of a summary is that people thought that reporting to both systems made some sense, and I don't think that the FDA is worried about swimming in too many reports or too much information, and that there was a sense that there might be a way in which one person reporting to both might be onerous. It also occurred to me that the communication between the two different sides, that is, the medical side and the respiratory technician or nursing side, might not be so perfect that everyone would know who was going to report which,

and so you actually might end up with them canceling one another out, thinking the other was going to do it, especially in the demise of a patient. The aftermath of that is not one where there's usually great communication about who's going to do what. So, in any case, I think that most people, I heard, were saying that reporting to both systems made sense, but -- Dr. Mink, maybe you want to start us off by just saying what you think about that question.

DR. MINK: I don't know. I agree with you. I think, you know, we don't want redundancy. We don't want confusion. But we want accurate tracking. So whatever, you know, works best. And I don't really know which would work best but I think that, you know, again, you don't want redundancy, you don't want confusion, but we want complete tracking.

DR. REED: Michael Reed. I revise that to reporting to either of the database and I agree with the statements that attempting to require both is unnecessary and may, in fact, diminish the reports -- the number of reports.

DR. SANTANA: This is Victor Santana. I actually -- I agree totally with what was just said. I think it should be either, not both.

DR. MCGOUGH: Jim McGough. I really don't have a strong opinion but it seemed to me that there was merit in reporting to both.

DR. ROSENTHAL: I agree with Dr. Reed.

DR. WHITE: Michael White. I think, as I stated before, either of the reporting systems should work.

DR. BAKER: Susan Baker. I'm going to defer to the FDA. You know what works best and where you get your best information, and you do a good job of using it, so...

DR. HUDAK: This is Mark Hudak. I agree that both pathways of reporting should remain open.

DR. LARUSSA: Phil LaRussa. I guess I would say I'll allow reporting to either system.

DR. DRACKER: Bob Dracker. I agree with dual reporting; however -- first of all, because I don't think you can always distinguish which is which. And so I think that's critical. The second, though, is I still think some reminders, some guidelines need to be given to the users of the device and therapy as far as what should be watched, especially after a history of adverse events.

DR. FRANCO: Israel Franco. I agree with dual reporting, again, for the same reasons that Dr. Dracker mentioned.

DR. GLASIER: Charles Glasier. I agree with dual reporting.

DR. WAGENER: Jeff Wagener. I agree that both systems should be available.

DR. WIEFLING: Bridgette Wiefling. I feel that one system or the other is fine for reporting.

MS. CELENTO: Amy Celento. I think either is fine. But I do want to say I have no familiarity with how anybody enters these reports, but I'm always in favor of the KISS principle. And if there would just be a check box as to how many databases you want to put this one report in, that would probably make it a lot simpler on any practitioner, respiratory therapist, anybody. But again, I have no familiarity with this, but the easier you make it for someone to file a report in any number of databases, I think, just the better it will be.

BACKGROUND INFORMATION ON SYSTEMIC JUVENILE

IDIOPATHIC ARTHRITIS (SJIA)

CHAIRMAN TOWBIN: Thank you all very much. So I think we're ready to move along now, and we're, I think, allowing an opportunity for us to hear from Dr. Schanberg, who's going to talk to us about the systemic treatment of juvenile arthritis. And Dr. Schanberg did her postgraduate training at Duke University. She's currently the division chief of pediatric rheumatology at Duke. She's an active researcher, a leading investigator, initiating clinical trials in pediatric systemic lupus erythematosus, juvenile onset arthritis, and pain in children with juvenile arthritis. She's also the principal investigator of a national registry for children with rheumatic disease. She's a founding steering committee member and now chair elect of the Childhood Arthritis and Rheumatology Research Alliance. So, welcome, Dr. Schanberg, and thank you for being here.

DR. SCHANBERG: Thank you very much. I was delighted to be asked to speak with you all since you guys are really considering some of the things that are of greatest concern to the pediatric rheumatology community, which is the safety of many of the very new, very terrific new products that are -- that we're all using regularly. So I have some disclosures.

So systemic JIA is diagnosed in children under the age of 16 who have inflammatory arthritis, but they are characterized by a lot of systemic features, and the picture shows some of them; that is, this very hectic fever, the rash that you see in this little boy, and serositis. These features are not found in any other type of arthritis and, in fact, the tendency now is to think about systemic JIA not really in the same grouping with JIA. It -- in fact, system JIA may be more like an autoinflammatory disease than it is like other subcategories of JIA. And the reason that this is important, and that I'm choosing to even start with focusing on this, is that it means that extrapolation from existing safety and efficacy data in either adults with inflammatory arthritis or in children with other forms of arthritis is really not possible, safely. For example, gold, which, thank goodness we don't have to use any more, but we were using when I first got trained, which dates me quite a bit, turned out to have whatever minimal efficacy it did in children with standard JRA, we called it back then, but really didn't work for kids with systemic JIA. And it actually turned out that it was dangerous in children with systemic JIA. And by the time I was -- I was being taught, we were strictly told that you cannot use systemic -- use gold in systemic JIA. That's just an example of how what might be safe

in one form of JIA is potentially not safe in a child with systemic JIA.

The disease has increased morbidity and mortality compared to other forms of JIA, and also has increased levels of cytokines compared to the other categories. Now, most of the categories of JIA have similar cytokine elevations but they are exponentially higher -- similar cytokines are exponentially higher in system JIA. Now, over the ages, systemic JIA has had a lot of very affected children who have not done well. And these are just some pictures of children pre-1940, that would be before steroids, the 1950s and 1980s, and then more recently in the 1990s and 2000s. However, since that time, this would all be pre-biologic, and I realized as I was putting this talk together that I didn't have a picture of a current child with systemic JIA. And that's because you wouldn't think of taking a picture of them because they are now doing well. They no longer look this. So the new drugs that have become available have dramatically changed the course for children with JIA and made being a pediatric rheumatologist much more fun. So the complications of systemic JIA include rash, fever, lymphadenopathy, which can be really significant, and in fact, this picture is sort of fun because you can see the lymphadenopathy in this little boy. If you can see under his axilla here, those are -- that big, bulky stuff, those are huge

lymph nodes, which these children get. They also get growth disturbance, as you saw in the other pictures; pericarditis, pleural effusions, anemia -- very significant anemia down to, you know, hemoglobins of 5. So if you see a child in an ED and they have a hemoglobin of 5, it's either cancer or systemic JIA [laughs]; thrombocytosis up into the one million kind of platelet counts; leukocytosis, 50,000, you can see white counts of, which is why we work closely often with our oncology friends, getting bone marrows on many of these children; misery -- these children feel worse than any other kids with rheumatic diseases. They get joint destruction, which is shown in this slide here. You don't have to be a radiologist or a rheumatologist to know that those hands look pretty pitiful. As well as they can get different types of avascular necrosis, particularly with the use of steroids. They have more pain than other children with arthritis, and they have macrophage activation syndrome as well as -- we're now recognizing they seem to get pulmonary hypertension. And I've highlighted those because we're going to talk a little bit more about them.

So macrophage activation syndrome in pediatric rheumatology. So MAS has been reported in all rheumatic diseases but is clearly most common in systemic JIA, which represents 80 percent of the cases of MAS in rheumatic disease -- childhood rheumatic disease. And the clinical spectrum is

anywhere from overt and life-threatening, and that prevalence is thought to be about 10 percent, versus subclinical MAS, which is just beginning to be discussed and written about, which is thought to be as high, perhaps, as 30 percent. It's basically lack of control of an exaggerated immune response and is related to familial hemophagocytosis seen in -- more in the oncology world. It's most -- we think of it as a cytokine storm, and there are both release of T-cell-derived cytokines as well as monocyte- and macrophage-derived cytokines. And you can see that this overlaps with a type of cytokines that are being blocked by many of the newer biologic agents. There's really no established diagnostic criteria for MAS in pediatric rheumatology. We often use elements of the current diagnostic criteria that the oncologists use. But in clinical practice, what we look for is an abrupt decrease in the sedimentation rate, abnormalities in LFTs, persistently high CRPs, and an increase in d-dimers. And as a clinical pearl, the arthritis actually often improves while this is happening. So this is just a cartoon that I adapted from Alexei Grom, who's considered an expert in MAS in rheumatic diseases; he's at Cincinnati. And right now we're finding more and more genetic abnormalities, mutations, in children who develop MAS. And these abnormalities may result in deficient cytotoxic cell function and expansion of macrophages, leading to the diminished ability to control viral

infections and causing a persistent source of antigenic stimulation. This all ends up with an escalated production of cytokines, stimulating macrophages, ending up in the clinical syndrome.

Moving onto the pulmonary complications of systemic JIA, there have been isolated case reports of pulmonary complications for quite some time, both in systemic JIA and adult-onset stills disease, including pulmonary artery hypertension, alveolar proteinosis, interstitial lung disease. But since 2008, there's just been a sense within the community that we have more cases of lung disease than we were used to seeing previously. And initially this was not in any sort of academic way. It was really something that, as clinicians, we just started seeing cases and wondering what's going on with this. Have we missed it before? What has been happening that might have changed it? And one of the things that comes up is the idea of biologics since that is around when we started using biologics to treat this. Since that time -- well, I'm going to get into some data about that a little further on in the talk. So the treatment paradigm for systemic JIA is changing. It's already changed considerably and continues to change. In the recent past, children have been treated with NSAIDs, lots of steroids, with all the related complications from steroids, including an inability to get them off of steroids. It's often

very difficult to wean them off. And methotrexate, which, while it has some benefit, has never been shown or thought to be as effective in children with systemic JIA as with other types of JIA. The new paradigm has biologics front and center with adjunctive use of NSAIDs, corticosteroids, and less and less, actually, methotrexate. So as the biologic age dawned in the early 2000s -- I mean 2003 or so, what we learned was that TNF inhibition is not as effective in treating systemic JIA as it is in other types of -- in other subtypes. And etanercept was the first of the biologic agents used to treat arthritis with great success; however, looking at subpopulation analyses from the big studies that were done, we saw that children with systemic disease really did not have the same response rate. More recently, we've used IL1 and IL6 inhibition, which affects dramatic improvement -- pretty amazing, actually. In fact, parents will tell you that after the child gets their first dose in the clinic, that by the time the child gets home, they feel better. It's very gratifying to all of us, but it's amazing how quickly it is. So, on the other hand, IL1, particularly, inhibition has not been shown to be that effective in other types of JIA. So these are just some of the studies that show the effectiveness of both IL1 and IL6 inhibition. Only IL6 inhibition is approved by the FDA for an SJIA indication. And I'm only showing some of the data for IL1 inhibition because the

slide deck for the FDA presenter includes some of those for the IL6 inhibition. And as you can see here, again, it doesn't take a lot of statistics to show how well this is working. Children get the dose and they're -- they immediately, their active joints go down, their white blood counts go down, their hemoglobins come up, their platelets go down, their sed rates go down, and it's truly amazing how quickly it happens. So with this, we're clearly doing something much more targeted.

This figure comes from data from the CARRA registry, and in my introduction it mentioned that I'm the PI of a national registry for children with rheumatic disease. And this use data comes from that registry. What you can see here is the change that I've been describing. And this is only over a 2-year period, because the registry just started in 2010. And in that time, the use of methotrexate has come down because the dark blue is 2010 and then the green is 2012. The use of methotrexate is coming down. The use of IL1 inhibition is going up, and the use of IL6 inhibition is also going up. I happen to know from relooking at this data that this is continuing even more since the indication for IL6 inhibition has come out. This also just looks at medication use patterns, again, from the same registry. And what you can see is that all the DMARDs and we -- methotrexate is the major DMARD, is coming way down , its use.

While the use of biologics here in the yellow is going up and the use of biologic as part of combination therapy is going up.

So I've told you about many of the good sides of the biologics and systemic JIA and alluded to the question whether they increase the risk of severe complications of disease such as MAS, pulmonary disease, infection, and death. So there is not as much data about this as we'd like, to put it mildly. There are conflicting reports about the use of the different biologics in MAS. So there are reports of both using the biologics to treat MAS successfully as well as MAS occurring when children are on the biologics. So this is still a question that's up in the air. We do know for sure that cytokine inhibition doesn't provide full protection for all children taking these medications against MAS, even in patients who seem to have well-controlled systemic JIA. So that raises questions that continue to be clinical and research questions, whether MAS is just determined by genetic variance, whether the biologics are changing the balance in the cytokine network in response to infection in a way that favors, promotes MAS, and leading to an exaggerated immune response to viral illness. Now, as far as the lung complications that I alluded to, again, since most of them have been reported since 2008, we're concerned about the role of biologics. And this is just a study -- from a study that is currently in press, led by Yuki Kimura at Hackensack.

The study cohort here was gathered from a listserv within the pediatric rheumatology community as well as through surveys sent out through the CARRA network, which is the Childhood Arthritis and Rheumatology Research Alliance, which includes 96 percent of all pediatric rheumatologists in North America. So that's where the study cohort came from. And then it was compared to children in the CARRA registry. And as you can see that there were clinical significance that more -- a higher percentage of children had been exposed to biologics. So this was the summary from the paper that's in press. Most of the known cases, as I mentioned, have been since the introduction of biologics, particularly maybe IL1 inhibitors, although the IL6 inhibitors are so much newer to our use we don't have as much information. The patients were more likely to have severe, uncontrolled systemic disease, and they were more likely to have MAS. And we are now instituting many places, including ours -- have instituted routine pulmonary screening in children with severe systemic JIA. We also believe that prospective systematic surveillance of pulmonary disease in all children with JIA is needed, regardless of medication exposure.

So how do we answer the pressing safety questions that I've raised, as well as ones that I haven't raised? So currently one of the major systems has been through post-marketing registries. And unfortunately the registries have too

few patients in them to really capture any of these relatively rare complications of systemic JIA, including, you know, for malignancy, for example, we figure that -- the data suggest that you need to follow a thousand patients to get one malignancy. And the registries in general are more in the 500-patient range. So -- and that's the larger ones. Initially they were 300. So it's very difficult to make determinations about these rare -- relatively rare complications with the number of patients that are currently being followed in the registries. In addition, there's limited comparator data. And since children with systemic JIA are already prone to some of these issues, if we don't have good comparator numbers, it can be very difficult to determine whether -- what the role of the drugs are. They also tend to be limited to the product of interest to date, but most of the patients get serial medications. They don't just get one biologic over the lifetime of their disease; they often get multiple biologics serially. There are also competing small projects, and since children are on a variety of biologics, they may go on one registry, then they're not available for a registry for a different product. There has been slow patient accrual and, in general, limited usefulness. And just, you know, obviously, I'm quite honest about my bias about the need to use more global registries, including the one that we currently have going, to address some of these safety issues.

We currently -- the registry has 62 CARRA sites activated. Even though we've only been collecting data since May of 2010, we already have over 8,000 patients enrolled, with 6,000 JIA patients. Out of those, 10 percent have systemic JIA. So we have 600 children with systemic JIA currently in the registry. The registry has been designed to be able to layer additional studies on so that they can serve as post-marketing safety surveillance as well as therapeutic trials, comparative effectiveness studies, and observational studies.

CARRA CoRe is an attempt to put together a consolidated safety registry, and this initially was started, in fact, by the FDA. And CARRA was asked to move this idea forward. We'd been working with the task force representing all the sort of players within our community, including the FDA and the EMA and registries in Europe. I think some of the advantages I've already alluded to, and that is that we are able to get rapid accrual of patients, to be able to answer the questions more quickly. We have -- are able to provide long-term follow-up, including into adulthood using a call center. We are going to have central adjudication of adverse events and central coding of adverse events and partnering with investigators, industry, patients, and government. So we have started the dialogue for a consolidated registry, including

talking with some industry partners, but finding this quite difficult to actually get off the ground.

So in conclusion, systemic JIA is a distinct entity separate from other forms of JIA. The new treatments, including the IL1 and IL6 inhibitors, have dramatically improved the lives of children with disease. The medication usage patterns for JIA are rapidly changing. Safety concerns for these medications, however, have not yet been adequately addressed, and this is frustrating both to parents and providers. The patient advocacy groups have this as their number one priority, is determining more -- know more about the safety of the medications that they're putting their children on. As reflected by an article in the Times, many of you might have seen about a boy with a thorn in his joint. I don't know if anybody read it, but that -- it was about a parents not wanting to put their kids on standard conventional medicines because of the lack of information about safety. We strongly believe within the pediatric rheumatology community that a multi-product registry such as the Consolidated Registry is scientifically the most rigorous way to address these concerns. And comparative effectiveness research of the treatments is needed to optimize care because we know the drugs work. We don't really know exactly how to use them and when to stop them.

These are just acknowledgements, including funders of the research that was -- that I presented today. And I would be delighted to answer any questions.

CHAIRMAN TOWBIN: So in the interest of time, I just want to remind people that I do want to move along a bit crisply. If there are some pressing questions for Dr. Schanberg, we can raise those at this time; otherwise I think we would move along to the presentation. So is there -- Dr. Dracker?

DR. DRACKER: I'll be brief, I promise. Number one, there are a number of cytokine storm-like illnesses that we're recognizing. CDC has come up with diagnostic criteria for some of the others, toxic shock-like syndrome, Kawasakis and others. I think part of the problem in collecting the data has been it would be nice if CDC came forward with diagnostic criteria for these patients. That's number one. The second is are toll-like receptors up- or down-regulated in these patients?

DR. SCHANBERG: I don't -- I would be -- I think they're up-regulated but I'm not a hundred percent sure.

DR. DRACKER: Something like TSLS is down-regulated because of cytokine storm. I was just curious.

DR. SCHANBERG: You know, I -- I don't know.

DR. DRACKER: Okay. That's all.

DR. SCHANBERG: Sorry.

DR. DRACKER: Quick.

CHAIRMAN TOWBIN: Thank you. Dr. Schanberg, thank you very much for sharing your -- oh, there was one more. Dr. Wagener, I'm sorry.

DR. WAGENER: Just one really quick question. On your slide showing the last three years of data on use, the GCI -- I assume is glucocorticoids. Have they been going up also?

DR. SCHANBERG: Yeah, that's -- we're not sure what to make with that. You've picked that out. It's hard to know what to make of that exactly. Many -- you know, we've actually been able to do a study where we even came up with a standardized way of tapering steroids, and from -- in many practices like mine, we almost never use steroids any more. We use the biologics without corticosteroids except perhaps as a very short bridge. So I'm not sure what that reflects.

DR. WAGENER: Because I was wondering if there's a combination issue here that people are using both the biologics and glucocorticoids and if maybe that's the reason why you're seeing some of this.

DR. SCHANBERG: Maybe, but they-- it's a little hard to -- we need more information to look at that more carefully.

CHAIRMAN TOWBIN: So that was very informative and very clear, Dr. Schanberg. Thank you very much. All right. So I think we're ready now to begin our -- to hear about Actemra.

Dr. Snyder is going to present to us. Dr. Reed is recused for this discussion. Dr. Cnaan has rejoined us, and Dr. Maldonado has left for the remainder of the day.

ACTEMRA (TOCILIZUMAB)

DR. SNYDER: All right. I'm presenting the pediatric focus safety review for Actemra, or tocilizumab. By now you're all familiar with the format for these presentations.

Actemra is an injection for intravenous use that was originally approved in January 2010. Actemra is an interleukin-6 inhibitor. A pediatric labeling change in April 2011 triggered this PAC presentation.

Actemra is indicated for use in adult patients with rheumatoid arthritis who've had an inadequate response to one or more disease-modifying, anti-rheumatic drugs, or for patients two years of age and older with system juvenile idiopathic arthritis, or SJIA. At the time of Actemra approval, studies in pediatrics were not completed. After approval, the sponsor submitted data for SJIA, which included pediatric patients aged two years of age and older. That pediatric labeling change is what triggered this pack review. There are outstanding post-marketing study requirements for a PK/PD safety and efficacy study in children from two years to 17 years of age with polyarticular JIA and a PK and safety study for children under

two years of age with SJIA. Reports for the study in polyarticular disease are due in March 2014 and for SJIA in October of 2014.

Dr. Schanberg has already talked a bit about SJIA. This slide includes a clinical presentation that may be seen with SJIA. The arthritis and fever may be accompanied by a characteristic rash, enlarged lymph nodes, hepatosplenomegaly, or serositis. And the classic lab testing for other types of JIA are not generally helpful with this type of disease.

The differential diagnosis includes malignancy, infection, inflammatory bowel disease, and connective tissue disorders. These patients tend to be very sick and half will go onto have persistent disease. The fevers and other systemic features resolve over time and arthritis becomes a predominant feature. Death rate is higher in these patients and is often attributed to infection. One trial was conducted in pediatric patients age two to 17 years of age to support the SJIA indication. The majority of patients in the trial were on methotrexate and corticosteroids at baseline. The study included a five-year open label extension. Most of the patients in the 12-week trial entered the long-term extension phase with 105 completing one year. Data from abroad on approximately 750 patients in short- and long-term clinical studies and post-marketing registries were used as supporting data. In the 12-

week control portion of the trial, the most common adverse events were upper respiratory tract infection, headache, *nasopharyngitis*, and diarrhea. Serious adverse events seen in the U.S. trial were macrophage activation syndrome, which we've already heard about, and fusion reactions, anaphylaxis, immunogenicity, decreased WBCs, decreased platelets, increased lipids, and increased liver function tests. There were six pediatric deaths seen in the studies that were used to support approval. These deaths occurred in patients on concomitant medications, who also had complicated medical histories that contributed to the cause of death. The studies supported labeling for ages 2 years and above.

Now we'll move on to the labeling changes relevant to this review. Pediatric information is sprinkled throughout various areas of the label. Dosage and administration includes dosing in SJIA. Warnings and precaution was updated to include changes in laboratory parameters in SJIA patients. These laboratory changes were similar to those seen in adults. In the Use and Specific Population section, the Pediatric Use subsection contains information regarding the basis of pediatric approval. This subsection states that safety and effectiveness in conditions other than SJIA or children under age 2 have not been established. Data on testing in juvenile animals is also

included. The Clinical Pharmacology and Clinical Study section include the pediatric study information that supported approval.

Now we'll move on to pediatric use. Over the cumulative time period from January 10 through June 2012, about 510,000 Actemra vials were sold from the manufacturer to the backdoor of various retail and nonretail channels of distribution in the U.S. From a sample of 95 pharmacies and 1,400 clinics, hospitals, and physician offices, about 6,000 patients had a prescription or medical claim for Actemra over this time period. The majority of these patients were age 18 years of age and older, accounting for approximately 98 percent of total patients. Patients age 2 to 17 years accounted for approximately 2 percent of total patients, and patients age 0 to 1 years accounted for less than 1 percent of total patients.

And over the same cumulative time period, pediatricians were the top prescribing specialty for patients age 0 to 17 years, while rheumatologists were the top prescribing specialty for patients age 18 years and older. Of patients who had a prescription or medical claim for Actemra, juvenile rheumatoid arthritis, otherwise not specified, was a top concurrent diagnosis in patients age 2 to 17 years, while rheumatoid arthritis was a top concurrent diagnosis in patients age 18 years of age and older.

This table includes the adverse events report submitted over the 30-month time period from the date of approval to June 30, 2012. There were 3,088 reports. Of the 3,088 reports, 118 were pediatric. There were seven pediatric deaths. Review of the 594 unknown age reports identified five pediatric deaths. This resulted in a total of 123 reports for review. There were eight duplicate reports. Three reports were excluded because one occurred in a patient over 17 years of age, and two reflected maternal exposure. This resulted in a total of 112 pediatric cases for analysis including 12 deaths.

Here are the characteristics of the cases broken down by age, serious outcome, indication, and duration of therapy. The majority of the cases were identified in the approved age range of 2 to 17 years with three cases under age 2. There were 12 deaths, as already discussed, eight life threatening events, 57 hospitalizations, one case of disability, and 31 cases identified as other serious outcome. Most of the cases were identified in the approved indication of SJIA. The mean duration of therapy was seven months with a range of 0 to 40 months.

Now we'll move on to discussing the 12 deaths. Here are the various diagnoses that were indicated as the cause of death. I'll discuss these in more detail on the following slides. As you can see, three of the deaths were contributed to

macrophage activation syndrome, and the other three cases were complicated by MAS, and these are indicated by the stars on this slide, although, overall MAS was not considered to be the cause of death for those particular patients.

We've already talked a bit about MAS, but I've also included some information here about it. MAS may be difficult to distinguish from SJIA disease flares or substance-like syndromes. The pathognomonic feature of this syndrome is seen on bone marrow examination which reveals numerous morphologically benign macrophages exhibiting hemophagocytic activity. Patients present with non-remitting high fever, hepatosplenomegaly, encephalopathy, and hemorrhage. 10 percent of SJIA patients develop overt MAS with 30 to 40 percent possibly having a subclinical form during disease flares. Here's a table that illustrates some of the clinical, laboratory, and histopathological features of MAS.

Now we'll move on to a description of the deaths. Please note on this slide and on subsequent slides unlabeled events are underlined. The first three cases were reported from a clinical trial in Indonesia. These patients reportedly died of MAS and were between 2 and 17 years of age. No other details were provided. Three additional cases were complicated by MAS. The first involved a 2-year-old with SJIA and MAS. The patient was treated with tocilizumab, dexamethasone, plasma exchange,

and cyclosporine. The patient then developed a suspected infection which progressed to vasculitis, respiratory failure, and renal failure, and the patient died. The patient had multiple medical complications that may have contributed to the outcome.

The second case complicated by MAS was a 7-year-old with SJIA who also had a history of MAS, disseminated intravascular coagulation, and hepatic failure. The patient was on tocilizumab for SJIA which was discontinued. The patient ultimately died of pulmonary hemorrhage.

The third case complicated by MAS was a 9-year-old who had been on tocilizumab for SJIA for three years. The patient developed MAS and pneumocystis pneumonia and was treated with antibiotics, pulse steroids, cyclosporine, and plasmapheresis. PCP progressed to hemopneumothorax and shock, and the patient died.

Now we'll move on to the other cases. A 6-year-old with SJIA died of sepsis. This patient had been on tocilizumab for two weeks at the time of death and developed gastroenteritis-like symptoms, was taken to the hospital, became unconscious, and died. The autopsy report confirmed a diagnosis of sepsis.

The second case was a 16-year-old with SJIA who also had history of right heart failure, pulmonary hypertension, and

pulmonary edema at the time of using tocilizumab. Tocilizumab was discontinued. The patient was then treated with steroids, antibiotics, diuretics, and then improved. Subsequently the patient developed MAS and was treated with cyclosporine. The patient died one year after tocilizumab was discontinued due to a cardiac arrest.

The next case was a 13-year-old with rheumatoid arthritis who was wheelchair-bound and had a history of chronic bronchitis, recurrent respiratory infections, and tracheotomy who presented to the emergency room with a UTI, tracheobronchitis, and worsening bronchospasm, and died. The patient had been on tocilizumab for six months at the time of the event.

Finally, in the last three cases a cause of death is not reported. The first patient was a 1-year-old preemie with a history of cleft palate, hypoplastic kidneys, and SJIA who had a complicated medical history with interstitial pneumonia and had a shock-like state just prior to death. The patient had received 13 doses of tocilizumab at the time of the event. The next two patients had SJIA and Still's disease respectively. Additional medical history and cause of death were not reported.

Now we'll move on to the serious nonfatal adverse events. The serious nonfatal adverse events are classified on this slide. Keep in mind, as mentioned before, that unlabeled

events are underlined. Of the 20 cases of serious infections, eight patients reported multiple infections. Unlabeled infections included infectious enterocolitis, mumps, osteonecrosis, parvovirus, and appendicitis. Most patients were on concomitant immunosuppressive agents that may have contributed to the development of infections. Actemra has a box warning for serious infections, including tuberculosis.

There were 13 cases of macrophage activation syndrome in patients with SJIA. MAS is known to be associated with SJIA. There were 11 cases of hypersensitivity reactions. There were two cases of anaphylaxis and three cases of possible anaphylaxis. Actemra is labeled for hypersensitivity reactions, including anaphylaxis and death.

Gastrointestinal events included three cases of enterocolitis, three cases of hemorrhage, one case of acute pancreatitis, and individual cases of intussusception, pneumatosis, ileus, and gastric perforation. In the three cases of hemorrhage, concomitant medications included steroids in all three cases and methotrexate in one case. Both these drugs are labeled for GI bleeding. In the case of acute pancreatitis the patient was also on prednisone and cyclosporine, both labeled for pancreatitis. The warnings and precautions section of Actemra labeling includes a risk of low platelets without bleeding.

There were eight hepatic events; five cases involved elevated transaminases. Actemra is labeled for transaminase elevations. There were two cases of hepatitis. One was a 16-year-old with SJIA and possible MAS who developed hepatitis 20 months after initiating tocilizumab. The patient was also on methotrexate, which is labeled for hepatotoxicity. The second case of hepatitis was an 8-year-old with a history of increased liver function tests who developed hepatitis two weeks after started tocilizumab. The patient was on multiple concomitant medications, including methotrexate and acyclovir, which is labeled for hepatitis and could have contributed to the event.

There were eight reported case of neurologic events. All were single cases, some of which are unlabeled. The warnings and precautions section describes a theoretical risk of demyelinating disorders, which was listed as a cause in one case. Given that single cases were reported, it is difficult to attribute causality to tocilizumab. There was one reported case of malignancy that was diagnosed two months after receiving the first dose of tocilizumab. Concomitant immunosuppressants included methotrexate and rilanocept and another interleukin-1 - an interleukin-1 inhibitor. The patient was on these drugs for 18 months prior to initiation of tocilizumab. The Warnings and Precautions section of Actemra labeling describes a theoretical risk of malignancy.

There were 29 remaining adverse events that were otherwise not classified. The most common events in this category included five cases of worsening or flares of rheumatologic disease and three cases of nephrolithiasis. The rheumatologic events were considered related to the underlying indication for use, and nephrolithiasis is a labeled event. The 21 remaining pediatric cases describe events that occurred only once, so it is difficult to assign causality to tocilizumab. No safety signals were identified in any of these single cases. And here's a list of the remaining serious adverse events described on the previous slide.

This concludes the Pediatric Focused Safety Review of AERS reports. Labeling includes approval on pediatric SJIA patients age 2 years of age and older. The majority of adverse events were labeled serious infection, MAS, and hypersensitivity. The majority of unlabeled events were associated with concomitant medications or underlying autoimmune disorders. No potential safety signals were identified. The FDA recommends continued routine monitoring. Does the committee concur?

And thanks to every on this slide for their help with this presentation.

CHAIRMAN TOWBIN: And thank you, Dr. Snyder, for that very nice presentation. So, comments? Dr. White.

DR. WHITE: Michael White. I'm sorry, I have selective amnesia for anything to do with Duke after the Duke-Carolina game last Saturday, but our first person -- our expert, I'm sorry -- presented concern about pulmonary hypertension being much increased since possibly associated with the increased use of biologic agents, and the data that we presented doesn't really uncover that concern for pulmonary hypertension. Do you have anything to do or any data that can help us resolve those two stands?

DR. SNYDER: Yeah. I know OSE may be able to comment on that. I mean, looking at these cases, we didn't see any of that. So, you know, we're looking at the reports.

DR. NIKOLOV: May I?

CHAIRMAN TOWBIN: Yes, please.

DR. NIKOLOV: My name is Nikolay Nikolov, and I'm one of the medical officers of the review division, and I'm also a rheumatologist, and I would like to address this comment maybe. This is relatively new information, and it would be really very important for -- since it was mentioned, it's based on the conversation on the LISTSERV. It will be important for the rheumatology community to publish this data so we can look at this. But based on the review of the original application and subsequent follow-up safety evaluations, this didn't really pan out as a major safety signal.

CHAIRMAN TOWBIN: Dr. Wagner.

DR. WAGENER: So I was just interested in a couple of quick points, but I thought what I found I would mention to the committee, and that is when I saw your numbers that there are 120 patients that have been prescribed this medication in childhood, and you have 112 SAEs, that's a pretty high frequency, and more importantly there were 12 deaths, which is 10 percent, simple math. It turns out that in 2008 the reported mortality rate from SJIA was 9 percent. So 10 percent mortality is not something extremely high in this condition, which, again, surprised me, but I thought it would be worth noting.

CHAIRMAN TOWBIN: Dr. Dracker.

DR. DRACKER: Did any of the cases have eosinophilia or hyper-IgE at all, do you know?

DR. SNYDER: You can ask OSE that question. I don't remember seeing that specific --

DR. DRACKER: Hyper-IgE or eosinophilia?

DR. CAMILLI: No. This is Sara Camilli; I'm a safety evaluator with the OSE. I'd also like to point out that most of the case reports that were reviewed were foreign reports, so that could be one reason that it appears that there's a large number of reports. Drug use just focuses on domestic.

CHAIRMAN TOWBIN: Thank you for that helpful comment. Any others? Then perhaps we're ready to address the question about concurrence. Dr. Cnaan, can we start with you?

DR. CNAAN: Yes, Avital Cnaan, I concur.

DR. MINK: John Mink, I concur.

DR. SANTANA: Victor Santana, I concur with continued routine monitoring.

DR. MCGOUGH: I concur. Dr. McGough.

DR. ROSENTHAL: I agree with continuing with routine pharmacovigilance.

CHAIRMAN TOWBIN: That was Dr. Rosenthal, by the way.

DR. WHITE: Michael White. I think I'm going to disagree with routine monitoring because I have great concerns about the data that was presented. The pulmonary hypertension has increased significantly in the last three to four years, and we don't have a good explanation for it, and there's apparent disconnect between the data that we have and what was reported by our expert. So I would actually like to ask that we do some sort of surveillance for pulmonary hypertension as a signal.

DR. BAKER: Susan Baker. I concur with Dr. White, actually. I was really concerned with the numbers that were presented, but it may be that you can't address that until the publications come out. So, hopefully that'll be fine.

DR. HUDAK: Mark Hudak. Yes, I concur with routine but also blending in some of the longer-term data, as it appears that some of these side effects take several years to manifest.

DR. CATALETTO: Mary Cataletto. I would actually like to see this come back to committee after there is more data. The numbers of children who have this disease are quite small, and although at this point I would concur, I think we certainly need more studies.

DR. LARUSSA: Phil LaRussa. I actually agree with Mary's comments about coming back to the committee. So, I don't know how you do that, but routine monitoring and let us know more about pulmonary hypertension.

DR. DRACKER: Bob Dracker. I do not concur. I think we're dealing with subsets of patients with a complicated disease process that I don't think we fully really understand.

DR. FRANCO: Israel Franco. I concur with Dr. White's comments that we should be looking closer at the pulmonary hypertension issue.

DR. GLASIER: Charles Glasier. I concur with Dr. White's comments also.

DR. WAGENER: Jeff Wagener. I'm not sure what it means to say concur, so I'm going to disagree with the FDA recommendation and suggest that, if possible, the FDA work with CARRA for this new group of medications recently introduced into

this disease process in a small number and come back to the committee in approximately two years with further information and data on this -- on potential side effects, including pulmonary hypertension.

DR. WIEFLING: This is Bridgette Wiefeling, and I disagree with the FDA's recommendation as well. I think it should come back to the committee.

MS. CELENTO: Amy Celento, and I disagree with the recommendation, and I agree with Dr. Wagener's comments. Thanks.

CHAIRMAN TOWBIN: So, just to summarize here, I think that the sentiment of the committee is that this does need to come back to us with more data, that working through the registry to learn a little bit more about this signal of pulmonary hypertension is what people would like. Also, to remind people that routine monitoring would mean that a signal here would still be something that would surface. It doesn't mean that, you know, people stop looking. So, obviously, if pulmonary hypertension were something that was seen over time, we would hear about that any way. But I think that people are saying that they would really like to have some of the information from this registry as going prospectively brought back to the committee in a couple of years or so. Dr. Yao, then Dr. Wagener.

DR. YAO: Yeah, I just wanted to point out, and Dr. Snyder reminded us that indeed there is some postmarketing requirement studies that were mentioned at the beginning of her presentation, and it's likely when those studies come in it would trigger, again, another safety review to bring before the committee anyway, but the points are all well taken.

DR. WAGENER: I would just --

CHAIRMAN TOWBIN: Dr. Wagener.

DR. WAGENER: It's not just the pulmonary hypertension but also the MAS and other things that you're looking for already. So it's -- thank you.

CHAIRMAN TOWBIN: So I think there's a need for some clarification here. Maybe if we could just check. So, how many people are saying that they do not concur with routine monitoring here?

DR. ELLENBERG: Keep your hands up.

CHAIRMAN TOWBIN: Dr. Cnaan, do you have a question?

DR. CNAAN: I'd like to raise a question, because my understanding of routine monitoring -- and I might have been wrong -- is because of what was presented right up front, that some studies are not complete, that by routine this would've come back to us, which is part of why I concur. So I'd like a clarification from the FDA. What are we voting on?

CHAIRMAN TOWBIN: Dr. Nelson or Dr. Hausman, do one of you want to say?

DR. HAUSMAN: FDA has to ask the committee what they're recommending. I have to turn it back, because, yes, routine monitoring means as part of the active process of what we do. If we have supplements come in, complete studies come in, they trigger labeling changes. We go through this process again, and in a year or three or four years this product would, in fact, come back to the committee.

DR. COPE: I think we'd like a clarification of this comment.

DR. NIKOLOV: One just additional clarification that the study -- the pivotal study that was based for the regulatory decision to approve the drug is still ongoing. The open label extension -- long-term extension is still ongoing, so still accruing data, and that would certainly be on our radar to look for the raised safety concerns, including pulmonary hypertension, and it would be really important to have the data also available to us from the pediatric community.

CHAIRMAN TOWBIN: So, if I understand this correctly, we really don't have to have a mutually exclusive choice here. In other words, one could have routine monitoring and have information brought back to the committee at some future date

when the studies were done. Is that correct? So, with that in mind -- Dr. Wagener?

DR. WAGENER: But that doesn't have a specific time limit on it, and if their postmarketing study is a five year long study, it could be five years from now before the company comes back with the results. It could be longer than that if they delay their postmarketing commitments. So I really think that this is something significant enough that we should give a date or a time, and that's why I suggested two years, which is probably not routine, but it does set a time.

CHAIRMAN TOWBIN: So would someone have language for a proposal for the committee to vote on about that?

DR. WHITE: I have a question first. Routine monitoring is you're going to monitor all your standard data sources, but we have this database that's being set up, this registry. Do you routinely have access to that registry as part of your monitoring?

DR. NIKOLOV: So, what I can tell you is that the FDA has been active advisor to the CARRA registry. We -- this is essentially a very recent initiative by the academic pediatric rheumatologists, and we certainly believe that collecting long-term data is important and informative to both prescribers and patients, and we believe that, in this respect, collecting these

data through a disease-based registry, not a drug-based registry, might be an additional tool to capture these events.

CHAIRMAN TOWBIN: Dr. White?

DR. WHITE: Dr. White -- Michael White. If I could then propose that we return to routine monitoring with the additional regular assessment of the CARRA database for other signals.

CHAIRMAN TOWBIN: Perhaps to be brought back in two years per Dr. Wagener's request?

DR. WHITE: Sure.

DR. NIKOLOV: Just one point, that some of these adverse events may take -- may have longer latency to accrue, so two years might not be reasonable to accrue enough events to even make sense out of the data.

DR. WHITE: If -- I would argue that if you have a signal now based on the CARRA registry for increased pulmonary hypertension over the last three years, two years might actually be too long, so I think two years is a very reasonable timeframe to look at it, and if you find nothing that's okay, but if you happen to uncover a signal in two years it might be very important for the use of these agents.

CHAIRMAN TOWBIN: Dr. Hausman.

DR. HAUSMAN: Yeah, I want to point out to the committee that FDA does not necessarily always have routine

access to all of the databases for various drug registries that are set up. We may -- I officially have to say I have no idea if we have access to this particular database. So, if we, in fact, do have access to it, it will be one of the tools that we can use, but it's not a question I can answer for the committee right now.

DR. WHITE: Then I will amend my statement.

CHAIRMAN TOWBIN: Please do.

DR. WHITE: Routine monitoring and request access to the CARRA database and use that information as appropriate, and bring the information back in two years as Dr. Wagener has suggested.

CHAIRMAN TOWBIN: Dr. Cnaan?

DR. CNAAN: I would like to address the timeline. I think it is important to set a timeline. I think we need to set it at a point where there is at least the prospect of having enough additional information for us to make a better determination of what we're looking at. I want to go back to the numbers. How many new prescribed cases are we expecting per year? Could anybody -- I'm not sure who could answer that, based on current numbers.

DR. WAGENER: So the timeline for the report today -- this is Dr. Wagener. The timeline for the report today was 30 months, and in 30 months there were 112 reported SAEs and 12

reported deaths. One would expect, unless there's some dramatic change, that you'll see a comparable number over the next two to 2.5 years.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: Well, I would argue that two years is a good period of time, because one thing we were told is that there is increasing use of these drugs. So we may actually see accelerated numbers compared to what we've seen before, and we may actually get our answer within that period of time. So I think two years is appropriate.

CHAIRMAN TOWBIN: So, allow me to restate Dr. White's proposal, and if I get it wrong, Dr. White, please correct me. But I think that what's before the committee is that we would say routine monitoring with a request to come back in two years with data from the CARRA registry or some sources that would help us gain some insight about the rates of pulmonary hypertension and MAS related to this class of drugs.

DR. WHITE: If it's available.

CHAIRMAN TOWBIN: Dr. Wagener.

DR. WAGENER: We could simplify this and just say continued routine monitor -- first of all, I think the FDA is doing a great job here. So I would say continue with your current plans for monitoring with an interim report and review in two years. However you get that, you get it.

CHAIRMAN TOWBIN: All right. So, can I just see a show of hands of people who would report return to routine monitoring with an interim report in two years? Good. Anyone think that is not a good idea? All right. So, do we need to go around and say our names and vote for this? Dr. Ellenberg is telling me it would be helpful, and, of course, we wish to be. So, Dr. Cnaan, if you would start us off.

DR. CNAAN: I concur with Dr. Wagener's recommendation.

DR. MINK: John Mink. I do too.

DR. SANTANA: Victor Santana. I agree with the motion.

DR. MCGOUGH: Jim McGough, yes.

DR. ROSENTHAL: Jeff Rosenthal, yes.

DR. WHITE: Michael White, yes.

DR. BAKER: Susan Baker, yes.

DR. HUDAK: Mark Hudak, yes.

DR. CATALETTO: Mary Cataletto, yes.

DR. LARUSSA: Phil LaRussa, yes.

DR. DRACKER: Bob Dracker, yes.

DR. FRANCO: Israel Franco, yes.

DR. GLASIER: Charles Glasier, I agree.

DR. WAGENER: Jeff Wagener, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

AMY CELENTO: Amy Celento, yes.

CHAIRMAN TOWBIN: Thank you all very much for a very nice collaboration with the committee and clear recommendation to the FDA.

DR. ELLENBERG: And, just real quickly, that -- your verbal statement was very helpful because that is recorded in the transcript. When we get a show of hands, that's not. So that's why I wanted to have you verbally state what your position is. Thanks.

LAMICTAL XR (LAMOTRIGINE)

CHAIRMAN TOWBIN: So I think that we're ready to move along to Lamictal XR, also known as lamotrigine. Just to let people know that Dr. Reed is recused on lamotrigine/Lamictal XR.

DR. SNYDER: All right. Let's go back. I'm also presenting the Pediatric Focused Safety Review for Lamictal XR or lamotrigine extended release. And here's the format for this presentation.

Lamictal XR is an enteric-coated tablet for oral use that was originally approved on May 29th, 2009. Lamictal XR is an antiepileptic drug, or AED. A pediatric labeling change in April 2011 triggered this PAC presentation.

Lamictal XR is indicated as adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization in patients 13 years of age and older, and for conversion to monotherapy in patients 13 years of age and older with partial seizures who are receiving treatment with an AED. The addition of the conversion to monotherapy indication triggered this PAC review. Lamictal XR comes in a variety of dosage strengths from 25 to 300 mg. Lamictal XR was presented at the December 2010 PAC. Review of the AERS cases indicated that breastfeeding infants who are exposed to significant amounts of lamotrigine through

breastfeeding. The PAC recommended that labeling be revised to include more information on exposure through breastmilk.

Now we'll move on to the labeling changes relevant to this review. As we look at the labeling, note that pediatric information is sprinkled throughout various areas of labeling. Dosage and administration includes the monotherapy indication. The Warnings and Precautions section has been updated to define multi-organ, hypersensitivity reactions under the drug reaction or eosinophilia and systemic symptoms or dress category. Postmarketing cases of aseptic meningitis have been reported in pediatric and adult patients taking lamotrigine for various indication, and this information has been added to labeling.

And as we previously discussed, based on recommendations from the December 2010 PAC and the use of specific population section, the Nursing Mother subsection has been updated to what is on this slide to what is on this slide. This section includes information from the literature on elevated blood levels in infants after exposure to lamotrigine through human milk. The labeling states that elevated blood levels in infants may be related to higher levels in mothers because of the increased dosages of lamotrigine used during pregnancy and because infants clear lamotrigine less effectively. Events such as apnea, drowsiness, and poor suckling are adverse events that may be seen. Labeling goes on

to state that infants should be closely monitored and infants blood levels be measured if concerns of toxicity arise. Human milk feedings should be stopped in infants with toxicity and caution used if lamotrigine is used in a nursing woman.

The Clinical Study section includes the pediatric study information that supported approval for the conversion to monotherapy indication for partial onset seizures. The Patient Counseling section includes information on dress, aseptic meningitis, and use while breastfeeding.

Now we'll move on to drug use. This table provides the total number of patients for Lamictal XR use in the U.S. outpatient retail pharmacy setting. Pediatric patients age 0 to 16 years accounted for 15 percent of total prescriptions and 12 percent of total patients for the review period. Pediatric patients 13 years of age and older accounted for about 62 percent of prescriptions. Nearly 40 percent of the patients prescribed Lamictal XR were in the unapproved age group of 12 years and younger.

Now we'll move on to the AERS review. This table includes the Adverse Events Reports submitted over the two year time period from July 1st, 2010, to June 30th, 2012. There were 270 reports. Of the 270 reports, 19 were pediatric. There were no pediatric deaths. Of the total 10 serious pediatric reports, there was one duplicate report. There were no excluded reports.

This resulted in a total of nine pediatric cases for analysis. As previously mentioned, there were no deaths.

Now we'll move on to discussing the adverse events. Please note that unlabeled events are underlined. Of the 10 reported cases, seven were breakthrough seizures in patients age 14 to 16 -- actually, that was of the nine reported cases. Three cases were confounded by hypoglycemia, irritability, rage, and mood changes depression. Hypoglycemia is not a labeled event, but the event was not well characterized and was not confirmed by a healthcare professional. There was one case of Stevens-Johnson syndrome in a 10-year-old hospitalized with a tracheotomy and pneumonia. The patient was also on zonisamide, which is also labeled for Stevens-Johnson syndrome. The last case was a 16-year-old who had symptoms of loss of vision, eyes rolling, lethargy, nausea, vomiting, and dehydration. The report states that the dose that was used was higher than recommended. The patient's symptoms reportedly resolved after reduction of the dose.

This concludes the Pediatric Focused Safety Review of Lamictal XR. No new safety signals were reported. FDA recommends continuing routine monitoring, which includes monitoring for breastfeeding-associated cases. Does the committee concur?

And thanks to all the people on this slide for their help with this presentation.

CHAIRMAN TOWBIN: Thank you, once again, Dr. Snyder. So, comments or questions that people might have? Dr. Wagener.

DR. WAGENER: Quick question on your last comment there. How are you monitoring for breastfeeding-associated cases?

DR. SNYDER: You can ask OSE; they said they would -- that was something that you were doing as part of your monitoring, correct?

MS. SIMMS: This is Kelly Simms from OSE. We monitor the adverse event reports that come across in our database.

DR. WAGENER: But the adverse event reports -- I'm not sure how they would pick up an infant of a mother who is on medication.

MS. SIMMS: Actually, when the signal was first caught when the label was updated, it was from a literature report which had been submitted into the adverse event reaction database from the sponsor. So those are also coming into the database as well, and we also routinely monitor literature as well.

CHAIRMAN TOWBIN: Dr. Cnaan?

DR. CNAAN: Actually, this was very interesting, but the regular report that we saw on others, I sort of agree with

Dr. Wagener. It was not relevant information to the question somehow, because the serious cases were on 16- or 10-year-olds. I'm not sure what routine monitoring is going to do for us, and hearing that this was picked from the literature to begin with, I think I'm at a little loss here. Where are we going?

CHAIRMAN TOWBIN: Dr. Simms, do you want to say anymore about that? Ethan? Dr. Nelson.

DR. NELSON: Sponsors are under an obligation to submit literature reports of any adverse events to the adverse event reporting system, so the literature is picked up not by the FDA reviewing the literature, which we might do anyway, but also picked up by the fact that the sponsors must report those adverse events.

CHAIRMAN TOWBIN: I think Dr. Wagener's concern was a little different, which is how a child, that is a child who is being breastfed and develops some toxicity, might be picked up.

DR. NELSON: It needs to be reported.

DR. HERSHKOWITZ: This is Dr. Hershkowitz.

CHAIRMAN TOWBIN: Thank you.

DR. HERSHKOWITZ: DNP, the neurology division. Now that we presently have it in the label, it is something that physicians will be aware of, this issue, and it's obviously -- it's very obviously in the label. So I understand your point. The point is the patient is the child or the breastfeeding

child, and the person may not make the association. But now I think that we have it in a label, I think there would be an awareness, and in routine monitoring people will understand this. And nonetheless, it is the label now.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: This is Geoff Rosenthal. You know, I just wanted to give you guys an attaboy for this, for the changes around lactation. You know, so frequently on the committee we'll discuss, you know, nuances of the label, and often we don't see the end product of that, but in this case I think the changes really are fairly profound in terms of the potential impact that they could have in informing users of this agent. So I just wanted to say I think you did a good job with the sponsor.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: So, I guess what we're really asking is, are there any plans or any thoughts about some sort of an active surveillance system where you would go out and look for cases rather than relying on the patient or the physician making the association?

DR. HERSHKOWITZ: We don't presently have plans, but I kind of thought, in a sense, that I dealt with that question previously. Let me ask you, what else in label can we do at the present time, other than put it in the warnings? And, you know,

I understand the point. You think -- you all think that there may be an underestimation of this because, again, the patient is the nursing child in this case, but really the person on Lamictal is the parent. But it seems to me that this is pretty straightforward, unless you think we're underestimating.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: Yeah, I don't think you can do anything more as far as the label goes, but I think, you know, one thought might be that you might require an active surveillance system either on the part of the manufacturer or on the part of some other agency like VSD or something like that, vaccine safety -- I'm sorry, not VSD, but on VAERS or something like that.

DR. HERSHKOWITZ: I think also there was an expression previously made that these are passive reporting, you know, and we can't go out there and -- it would mean that we'd have to inform doctors this is a very big thing that they ought to on lookout, you know, short of a label really saying that they ought to look out for it, but that they ought to be on the lookout. Now, let me ask -- I'm not a pediatrician, but let me ask the pediatricians, when a woman is breastfeeding and a child seems unusual, intoxicated or lethargic, do you look at the medications that the mother is on?

CHAIRMAN TOWBIN: Dr. Santana, would you like to answer?

DR. SANTANA: Yes. I mean, yes. But I wanted to get back to the issue of -- so the label's been changed, right? But when the pharmacist gives the woman the medication, is there any additional information related to this that should be given? That's what I think we're getting at. We're not really getting at the label because we can't change much on the label. The transmission of that information, I think, is what the committee is --

DR. HERSHKOWITZ: There is a MedGuide that's required, and I'll see -- this is the MedGuide for Lamictal. Lamictal has also changed as well as XR, and let me -- this is probably the answer to the whole conundrum, and let me see if I could find the part in the MedGuide which discusses this.

CHAIRMAN TOWBIN: While you look, would it be okay if we had other comments? Because I think there are a couple of other.

DR. HERSHKOWITZ: That's fine.

CHAIRMAN TOWBIN: Thank you. Dr. Mink.

DR. MINK: I just wanted to point out there are actually a couple of large-scale surveillance studies going on on the effect of both use of anti-epileptic medications during pregnancy and during breastfeeding, NIH-funded studies that are

-- there is one that just started this November that's going to recruit somewhere between 500 and 1,000 pregnant women with epilepsy on a variety of antiepileptics. So, I don't know if there's, you know, what the process of the FDA would be to tap into those data as they come out, but I think that that's a wonderful way to get at some of these questions.

CHAIRMAN TOWBIN: Thank you for that. Dr. Rosenthal.

DR. ROSENTHAL: Geoff Rosenthal. My comment might be more germinal even than Dr. Mink's comment, but I noticed in the label that there is a registry for pregnant women who are taking Lamictal, and it may be possible to build on that to try and understand some of these lactation-related exposures and potential effects.

CHAIRMAN TOWBIN: Dr. Hershkowitz, we'll come back to you then.

DR. HERSHKOWITZ: The registry is principally for teratogenesis. You're talking about the Massachusetts -- the Harvard-based registry, Lou Holmes [spelled phonetically].

DR. ROSENTHAL: North American antiepileptic drug.

DR. HERSHKOWITZ: I think we at times spoke to Lou Holmes, and my impression is it concentrates on teratogenesis. Anyway, if you'd like me to read some of the wording in the MedGuide.

CHAIRMAN TOWBIN: Please do.

DR. HERSHKOWITZ: Let's see. Something funny here. Where does this sentence start? I guess it says, "Breastfeeding: Lamictal XR passes into breastmilk and may cause side effects -- " [coughs] -- I'm sorry -- "effects in breastfeeding babies. If you breastfeed while taking Lamictal XR, watch your baby closely for troubled breathing, episodes of temporarily stopping to breath, sleepiness or poor sucking. Call your baby's healthcare provider right away if you see any of these problems. Talk to your healthcare provider about the best way to feed your baby if you take Lamictal XR."

CHAIRMAN TOWBIN: Thank you for that. So, I see some nodding of heads. So, are there other comments before we come to the vote? No. So it looks like we are ready. Ms. Celento, would you mind starting us off?

MS. CELENTO: I concur.

DR. WAGENER: Jeff Wagener, I agree.

DR. GLASIER: Charles Glasier, I agree.

DR. FRANCO: Israel Franco, I concur.

DR. DRACKER: Bob Dracker, I concur.

DR. LARUSSA: I'm sorry. I think I have to disagree. And what I would say is that I would like to see the FDA hook up with the active surveillance studies that are going back and report back to the committee in an appropriate time period, and I'll leave that up to you.

DR. CATALETTO: Mary Cataletto, I agree.

DR. HUDAK: Mark Hudak, I concur.

DR. BAKER: Susan Baker, I concur with routine monitoring.

DR. WHITE: Michael White, I concur.

DR. ROSENTHAL: Geoff Rosenthal, I do as well, but I do appreciate Dr. LaRussa's comment regarding trying to actively identify data sources and tap into them.

DR. MCGOUGH: Jim McGough, I concur.

DR. SANTANA: Victor Santana, I concur with routine -- going back to routine monitoring.

DR. MINK: John Mink, I concur.

DR. CNAAN: Avital Cnaan, I concur with the addition of coming back with data are available on the NIH funded studies.

CHAIRMAN TOWBIN: Good. So it seems that we have a recommendation to return this to routine monitoring, although some members of the committee also would like to have data back, perhaps from this NIH study or other sources, to understand a little more about the rates for this particular problem and adverse effect. And just to say, Dr. Wiefeling had stepped away during this time and did not vote.

All right. So it looks as if we've earned ourselves a little bit of a break. So I'd like to reconvene in 10 minutes,

if we could, and hopefully we can stay on pace here, and move on to paliperidone.

INVEGA (PALIPERIDONE)

CHAIRMAN TOWBIN: All right. I think that we're ready to go back into our discussion -- or last drug for discussion. And we're pleased to have Dr. Karesh talk to us once again. Dr. Karesh, thank you. Dr. Karesh is a pediatrician who received her medical degree from the Medical College of Virginia and completed her internship and residency at Children's Hospital of Pittsburgh. Prior to joining the pediatric and maternal health staff in 2008, Dr. Karesh worked as a pediatric hospitalist at Inova Fairfax Hospital in Fairfax, Virginia, and she also worked as a pediatrician for Kaiser Permanente, both as a general pediatrician and a hospitalist. Dr. Karesh is going to talk to us about Invega, also known as paliperidone.

DR. KARESH: Good afternoon. I moved the microphone up; can you hear me okay? All right. Here's the outline that you are all familiar with. Invega, an atypical antipsychotic, is approved as extended release tablets to treat schizophrenia in patients 12 years and older and schizoaffective disorder in adults. The sponsor is Janssen Pharmaceuticals. Invega was originally approved December 2006, with the pediatric labeling changes occurring in April 2011. Please note risperidone is a related product in that it is another atypical antipsychotic and it is metabolized to paliperidone. Risperidone will come up again in a few moments.

The pediatric written request was for the treatment of schizophrenia and included a nonclinical juvenile rat study. In adolescents, a PK study, a safety and efficacy study, and a long-term safety study. In the juvenile rat paliperidone study, no adverse effects were seen at plasma levels similar to expected exposures in adolescents. In female rats impairment of performance of learning and memory were seen at levels three times higher than the expected adolescent exposures. This impairment was reversible in the recovery period.

The other nonclinical toxicology study I wanted to mention involved juvenile dogs receiving not paliperidone, but risperidone. This is relevant to today's discussion because, as I mentioned earlier, risperidone is metabolized to paliperidone. Decreased bone length and density were seen at levels higher than the maximum recommended human dose of risperidone. A delay in sexual maturation was seen at all dose levels, including levels consistent with human exposure. In female dogs the bone and sexual maturation effects showed little or no reversibility after a 12-week drug-free period.

Now we'll discuss the pediatric PK study. This was an open-label study to evaluate the safety and PK of single and multiple doses of paliperidone. Peak plasma concentrations were reached approximately 24 hours after a single dose and steady state concentrations were reached within four to five days of

dosing. The efficacy of Invega in adolescents with schizophrenia was established in a six-week, double-blind placebo-controlled study over the dose range of 1.5 to 12 milligrams per day. The primary endpoint was a mean change from baseline to endpoint in the positive and negative syndrome scale for schizophrenia total score.

Overall, this study demonstrated the efficacy of Invega in adolescents with schizophrenia in the dose range of 3 to 12 milligrams per day. Doses within this broad range were shown to be effective. However, there was no clear enhancement to efficacy at the higher doses. Although paliperidone was adequately tolerated within the dose range of 3 to 12 milligrams per day, adverse events were dose related.

In this study there were no fatalities. Four patients experienced treatment emergent serious adverse events in the paliperidone groups, two schizophrenia and one each agitation and Mallory-Weiss syndrome. For comparison, one patient in the placebo group experienced a serious adverse event.

There is an ongoing open-label safety trial of paliperidone in adolescents. As of September 2010, there were no fatalities and the most common serious adverse event was schizophrenia.

Now that we've discussed the pediatric relevant studies, we'll discuss pediatric labeling. Subsection 1.1

states that the efficacy of Invega and schizophrenia was established in three six-week trials in adults and one six-week trial in adolescents, as well as one maintenance trial in adults. Subsection 2.1 provides adolescent dosing information. Subsection 5.6 provides data on change in fasting glucose and fasting lipids. This subsection also provides data on the mean change in body weight and the proportion of subjects with greater than or equal to seven percent gain in body weight. In general, dose-related trends in hyperglycemia, dyslipidemia, and weight gain were seen in adolescents and were consistent with both adult data and atypical antipsychotics as a class.

Section 6, Adverse Reactions, presents the overall adverse reaction profile in 6.1 and lists the adverse reactions reported by greater than or equal to 2 percent of adolescents, which includes extrapyramidal symptoms in 6.2. Subsection 6.4 states that among the adverse reactions in the adolescent trial, only dystonia led to discontinuation. Subsection 6.5 lists the dose-related adverse events tachycardia, akathisia, extrapyramidal symptoms, somnolence, and headache. Subsection 6.7 discusses extrapyramidal symptoms and states that the instance of EPS-related adverse events in the adolescent trial were similar to the adult trials and that there were higher incidences of dystonia, hyperkinesia, tremor, and Parkinsonism in the adolescents.

The Pediatric Use subsection of labeling summarizes the results of the adolescent study we discussed earlier. It states that the safety and effectiveness have not been established for the treatment of schizophrenia in patients less than 12 years of age or schizoaffective disorder in patients less than 18 years of age. It describes the adverse findings of the juvenile rat study with oral paliperidone and the juvenile dog study with oral risperidone, both of which we discussed earlier. And it states that the long-term effects on growth and sexual maturation have not been fully evaluated in children and adolescents.

Subsection 12.3, Clinical Pharmacology, Pharmacokinetics, Special Population Adolescents, states that paliperidone systemic exposure in adolescents weighing greater than or equal to 51 kilograms was similar to that in adults, and that in general the pharmacokinetics were comparable between weight groups, and age did not influence the paliperidone exposure. Finally, the adolescent efficacy study, which we discussed earlier, is described in 14.1.

Now that we've discussed the pediatric-relevant studies and labeling, we'll discuss use and then the AERS cases. This slide graphically presents a comparison of the Invega and risperidone pediatric use. Risperidone, as we've discussed, is another atypical antipsychotic and is metabolized to

paliperidone. Risperidone is indicated for the treatment of schizophrenia in adolescents and adults, as monotherapy for the treatment of acute manic or mixed episodes associated with bipolar I disorder in patients 10 years and older, or adjunctive therapy for bipolar one disorder in adults, and the treatment of irritability associated with autistic disorder in patients 5 years and older. The blue bars are the total risperidone use, and the yellow bars are total Invega use. The respective pediatric use are shown by the green and purple lines. Overall, 9 million risperidone prescriptions and 540,000 Invega prescriptions were dispensed in 2011. The pediatric population accounted for 22 percent of the risperidone prescriptions and 11.5 percent of the Invega prescriptions.

This slide shows the breakdown of Invega drug use in the U.S. outpatient retail setting between January 2007 and June 2012 cumulative. About 1 percent of the pediatric prescriptions were in patients 0 to 5 years of age, about 35 percent were in patients 6 to 11 years of age, and the remaining, about 64 percent, were in patients 12 through 16 years of age. Therefore, about 36 percent of the pediatric prescriptions, not of the overall use, were in the unapproved age group.

The top prescribing specialty for Invega was psychiatry, and pediatricians accounted for less than 1 percent. The top diagnosis code for patients 12 through 16 years was

other emotional child disorders; and the top diagnosis code for patients 6 to 11 years was ADD for the ICD-9 codes analyzed in the survey data. The use was too low to be able to capture diagnosis code data for patients 0 through 5 years of age.

This slide shows the total number of paliperidone adverse event reports since the pediatric approval. There were 153 pediatric reports total, of which 88 were serious and none were fatalities. Of the 88 total pediatric reports, seven were duplicates. Then, of the remaining 81 reports, four were excluded because they were actually adult patients or miscoded as paliperidone. That leaves 77 pediatric serious cases, no deaths. Of these 77 pediatric serious cases, the gender was known for 76 of the cases and there were approximately twice as many males as females. The age range for the 77 patients is shown on the slide. Of these 77 pediatric serious cases, 24 were unlabeled adverse events and the remaining 53 were labeled. We'll discuss each of these two categories of adverse events.

First, the 24 unlabeled pediatric serious adverse events. All 24 were confounded by comorbidities or concomitant medications, or the cases provided insufficient information to assess relationship between paliperidone and the events, or were accidental exposures.

This slide lists the types of these 24 serious nonfatal, unlabeled adverse events. We'll be focusing today in

the adverse events that occurred in more than one patient, starting with a discussion of the eight psychiatric cases. Of the eight psychiatric serious unlabeled pediatric adverse events, six involved aggression or belligerence, one depression, and one disorientation. All eight events may have been associated with the underlying psychiatric illness, or confounded by concomitant medications. As I mentioned earlier, we'll concentrate on the adverse events that occurred in more than one patient. So we'll discuss the six aggression or belligerence cases in detail.

For all the cases I've followed the PAC slide convention of underlining the unlabeled adverse events. This slide describes the case of a 6-year-old male with a history of violence, ADHD, and probable bipolar disorder. He experienced aggression and suicidal ideation while taking paliperidone, six milligrams, to treat ADHD; and 10 days after his concomitant lisdexamfetamine was switched to dexamethylphenidate. The patient's dexamethylphenidate dose was then increased, divalproex was started, and the paliperidone was continued. The outcome was not specified. Lisdexamfetamine and dexamethylphenidate are labeled for an association with aggression.

This slide describes two similar cases. Two males, ages 8 and 11, both experienced defiance and irritability after starting paliperidone three to six milligrams daily to treat

disruptive behavioral disorder. The 11-year-old was receiving the paliperidone also to treat bipolar disorder. In both cases the paliperidone was withdrawn and risperidone, which they'd both had previously been on, was restarted. The outcome for the 8-year-old was that the adverse events were not as pronounced, and the 11-year-old recovered.

Next, we'll talk about the case of a 10-year-old female. She had a history of a possible bipolar disorder. She experienced aggression and suicidal ideation while receiving paliperidone, three milligrams daily, for post-traumatic stress disorder. The paliperidone was continued and the patient had not recovered. Her concomitant medications include valproate, which is labeled for an association with aggression.

This slide describes the case of a 15-year-old male who was taking paliperidone and aripiprazole to treat schizoaffective disorder and desmopressin nasal spray to treat bedwetting. He refused his medication, became belligerent, and was hospitalized. Please note that aripiprazole is labeled for an association with aggression.

The last of the six aggression or belligerence cases involved a 16-year-old male who experienced aggression, frustration, anger, and violence 25 days after starting paliperidone, six to 12 milligrams, to treat schizophrenia. The patient was hospitalized due to aggression, paranoia, and

auditory hallucinations. His paliperidone was continued. His concomitant medications were lorazepam, which is labeled for an association with aggression, and benztropine.

As I mentioned earlier, there were seven accidental exposure cases. The age range was 2 to 5 years. The most serious of these cases involved a 2-year-old female who ingested five three-milligram paliperidone tablets. The patient was treated in the emergency room with activated charcoal and was admitted to the pediatric intensive care unit for overnight observation. She was discharged the next day. In this case the patient's father reported a failure of the child-resistance mechanism saying, "Sometimes the cap worked and locked properly and other times it spun right open." Labeling includes information on over-dosage, including that appropriate supportive measures should be instituted with close medical supervision and monitoring.

There were two reports of tics, one in a 5-year-old male with a history of Tourette's syndrome and ADHD who experienced a reemergence of tics, along with profuse sweating when running, oculogyria, somnolence, fatigue, increased appetite, swollen face, orthostatic hypotension, and weight gain. His concomitant medications were pimozide, reboxetine, risperidone, and sertraline.

The other case involved a 7-year-old male who experienced tics in his head and neck, a finger tumor treated with outpatient surgery, bones in his back which crunched and cracked like an old man, violence, and growling. The paliperidone was stopped after approximately three years, and the patient recovered from the tics.

This slide lists the other serious unlabeled adverse events that we didn't yet discuss. There doesn't seem to be a pattern with these cases, as the events occurred singly. There was one case each of hypothyroidism, decreased blood glucose, myocarditis, increased diopter and weight increase, acute renal failure, multiple complaints, including swollen prostate and DBT.

Now that we've discussed the unlabeled adverse events, I'm going to give a quick overview of the adverse events that are labeled and the related labeling. There were 53 labeled adverse events, 25 of which were CNS-related, seven metabolic, six psychiatric, four endocrine, four immunologic, and seven miscellaneous. Specifically, two were neonatal withdrawal syndrome, two overdose, two priapism, and one rash. I will show you, over the next several slides, where the labeled adverse events are included in labeling.

This slide lists the type of CNS adverse events that were reported and shows where those adverse events are included

in labeling. Dystonia is in the adverse reaction section of labeling. General extrapyramidal symptoms in somnolence are in the adverse reactions used in specific populations and over-dosage sections. And tardive dyskinesia, neuroleptic malignant syndrome, and convulsion, labeled as seizure, are included in the Warnings and Precautions and Adverse Reaction sections of labeling. Convulsion is also in the over-dosage section.

This slide shows where the metabolic and psychiatric adverse events are labeled. For example, weight gain, self-injurious behavior, which is captured under suicide, suicide attempt, and cognitive disorder are all labeled under both Warnings and Precautions and Adverse Reactions.

This slide shows where the endocrine and immunologic adverse events are labeled. Hypoplastic anemia, gynecomastia, and anemeia are in Warnings and Precautions and Adverse Reactions. Hypersensitivity is a contraindication.

Finally, this slide lists the seven miscellaneous adverse events and where they are included in labeling. So this concludes the pediatric focus safety review. No new pediatric safety concerns were identified. FDA recommends returning to routine monitoring. Does the committee concur? I would like to acknowledge the folks listed on this slide. Thank you.

CHAIRMAN TOWBIN: Thank you, Dr. Karesh. So, comments or questions that people might have? Dr. LaRussa.

DR. LARUSSA: So, I have three related questions related to gender. Can I do all three? They'll be short.

CHAIRMAN TOWBIN: It's totally all right.

DR. LARUSSA: Okay. So, slide number 7 where you talk about the juvenile dog study and you talk about decreased bone length and density seen at higher levels, are those -- I was a little confused there. Do you mean higher levels there of drug with the same dose or higher doses resulting in higher levels?

DR. KARESH: Rather than misspeak, I'll turn it over -- is there someone from pharm tox here today? Thank you, obviously.

CHAIRMAN TOWBIN: Yes, if you could introduce yourself.

DR. CHALECKA-FRANASZEK: Yes, my name is Elizabeth Franaszek, and I --

CHAIRMAN TOWBIN: Oh, I think what we're going to ask you to do is to step over to the table and use the microphone there. Unfortunately, that one does not seem to be working. Thank you.

DR. CHALECKA-FRANASZEK: So, questions related to clarification of exposure. Simply, at exposures expected or obtained so far in pediatric population at the same level of exposure in animals, there are no adverse effect on bones.

DR. LARUSSA: What about at the higher levels? And --

DR. CHALECKA-FRANASZEK: Yes.

DR. LARUSSA: -- how much higher were the levels?

DR. CHALECKA-FRANASZEK: At the exposures approximately three to four fold higher, there are different effects on bones, but I will --

DR. LARUSSA: Okay, so let's -- let's go back, then, to my question. Were -- so there are two ways of getting higher levels. You either give a higher dose or there are some people who at the same dose who end up with higher levels.

DR. CHALECKA-FRANASZEK: I mean, animals were tested at different dose levels, and exposure in animals, I mean, you see. And you see what's compared to exposures in pediatric population.

DR. LARUSSA: So, I guess what I'm asking is, did the animals get different doses or they got the same dose?

DR. CHALECKA-FRANASZEK: They got different dosages because of course they have different size, but we compared --

DR. LARUSSA: Maybe I'm not saying this clearly.

DR. CHALECKA-FRANASZEK: Yes.

DR. LARUSSA: Did -- were the animals given more than one dose to test the effect of different doses in the animals? So, did they get, let's say three milligrams, five milligrams --

DR. CHALECKA-FRANASZEK: Yes, of course.

DR. LARUSSA: Okay.

DR. CHALECKA-FRANASZEK: There was always in nonclinical studies we administer several different dosages.

DR. LARUSSA: Okay, so, with the higher doses, how much higher were the higher doses than the regular doses; the ones that resulted in the bone abnormalities? So it says here -
-

DR. CHALECKA-FRANASZEK: I don't remember exact dosages, I mean, non-effect dose, I think, was 125 milligrams in dogs, and dogs with an effect on bones was five milligrams.

DR. LARUSSA: Okay.

DR. CHALECKA-FRANASZEK: Most likely. But I would like to point out that effects on bones were really small. We thought that it's important to include those effects in labeling because they were obvious, but they were small. Decreases in bone density and length were about 10 percent comparing with control, 10 to 12 percent. So they were not very large.

DR. LARUSSA: Okay, so, my next question is on slide 12, and this is a short one. You talk about this ongoing safety trial. When will the results of that be done, available?

DR. KARESH: I'm hesitating because I am, I guess, restricted to public information, and in that capacity I'm not sure what I'm permitted to say. Defer to you.

DR. LARUSSA: So, just a ballpark idea so we know when you can come back to us with more information.

DR. HAUSMAN: Is that being done under a PMC or a PMR?
Because if it's being done under a PMC or a PMR, we --

DR. KARESH: It was part of the written request.

DR. HAUSMAN: Oh, it's part --

DR. KARESH: Bob, I defer to you if you want to say.

DR. DRACKER: We very recently got -- have gotten most of the data within the last two weeks and we've started looking at it. So, we really have no -- we really don't have an analysis currently yet to discuss.

DR. LARUSSA: Do you have any idea when you could get back to us with that data?

DR. DRACKER: We're actually working on it, probably within -- we don't really. Yeah, it's uncertain, but it is actively being reviewed.

DR. LARUSSA: And the last question. Slide 26, there is -- in cases where you knew the gender, there was a 2-to-1 ratio of males to females. Do you have any idea how that sorts out with the gender ratio in use?

DR. MINK: If I can answer that. For the disorders or the conditions these are used for, that's the usual. There's much more preponderance of males in that age group that need these sorts of interventions.

DR. LARUSSA: So that's what I'm trying to get at, is the --

DR. MINK: I think that's probably reflective of the use.

DR. LARUSSA: So, is the ratio 2-to-1, or is the ratio of males to females higher?

DR. MINK: It's certainly higher in males versus females. I wouldn't know the exact ratio.

CHAIRMAN TOWBIN: Dr. McGough is doing a good job of fielding that question. I think that I just might add it's going to depend a little on the diagnosis. If one were thinking about things like autism spectrum disorders, that ratio would be even higher. For schizophrenia it may be a little bit lower.

DR. LARUSSA: So the reason why I'm asking that question is, some of the previous information pointed to abnormalities in women, and you might -- you need to know the ratio of use to see if the ratio of adverse events is going to be altered, and maybe there's a gender issue that has to be addressed.

CHAIRMAN TOWBIN: Dr. Yao, did you want to make a comment here? I'm sorry.

DR. YAO: I just wanted to provide some clarification to Dr. LaRussa's first question. And in the labeling I note that it says that juvenile dogs are treated for 40 weeks with oral risperidone, which is extensively metabolized of paliperidone in animals and humans. And the doses that were

evaluated in that juvenile dog study were 0.31, 1.25, and 5 milligrams per kilogram per day, so it's sort of fold increases. And that it says here decreased bone length and density were seen with a no-effect dose of 0.3 milligram per kilogram per day, which produced plasma levels of risperidone plus paliperidone, which were similar to those in children and adolescents receiving the maximum recommended human dose of risperidone.

CHAIRMAN TOWBIN: Dr. Santana.

DR. SANTANA: So I noticed that when presented the utilization of prescription, that the patients that were less than 5 years of age were only about 1 percent of the share. But when you look at the 77 cases of serious adverse events, they represented about 15 percent of the cases, one out of six. So, my -- and I understand that may be numbers and things like that, I don't want to get into that. What my question is, are the side effects that the younger kids having different from what the older kids are having? Because that would be something of importance to practitioners and to patients. Do we get a sense that what's happening to the younger kids in terms of their side-effect profile is different from the older kids, who are, you know, the label says you can use it?

CHAIRMAN TOWBIN: It appears that someone has an answer for us.

MS. SALAAM: Hi, I'm Tracy Salaam, a safety evaluator in the division of pharmacovigilance. It appears that the side-effect profile in the younger patients is consistent, but I will point out that several of the cases for the younger children were the accidental exposure cases.

DR. SANTANA: I thought there was only one of those; is that correct? Was there more than one?

MS. SALAAM: No, there were seven.

DR. SANTANA: So that may be it.

MS. SALAAM: Correct.

CHAIRMAN TOWBIN: Dr. Cnaan.

DR. CNAAN: Yes, I want to go back to the male/female issue. I wondered whether the drug utilization data has that information, because it has age. Does it also have gender? You might not have it here; I'm just asking generically.

DR. KARESH: I would defer to the use reviewer.

DR. CHAI: Yes, generically, we can obtain it, but it wasn't provided in this review. We didn't include --

DR. CNAAN: Okay. And the other question I have is, you have prescriptions separately from patients. Is there any way to get from this database something about exposure, average exposure, that is not so much in dose, but in duration?

DR. CHAI: That would require another separate study that wasn't done in this review. And you're talking about a duration of use type study?

DR. CNAAN: Yeah, I mean, you can't know if somebody didn't use it any more, but at least based on the prescription data, how much it was prescribed for. Obviously, the use is some percentage lower than that because people stopped.

DR. CHAI: Yes. It wasn't included in the review, but, I mean, you can put that forward as a recommendation from the committee, but --

DR. CNAAN: Okay.

CHAIRMAN TOWBIN: Dr. White.

DR. WHITE: Michael White. Sometimes I'm not sure what I'm supposed to read and what I'm not, but the statistical review that was provided for the original labeling is a little peculiar and difficult for me to understand. It looks as if, first of all, this is a multi-cultural study. And is the diagnosis of schizophrenia the same in Romania, India, Russia, the United States, and there was one other site. Can you use that and the response to medications in those different cultures in the same way to evaluate the data that's given? And I'll ask these guys because they're much better at that than I am. And then the second issue I had is that under 51 kilos, the dose response is nothing low dose, great response medium dose, and no

response at high dose. And then when you go to the 51 -- greater than 51, the response was no response and the high and medium were the same. Now, in most instances when one gives drugs, the more the better, particularly if you're looking for responses of psychiatrists. And there's nothing on the label to reflect this peculiar dose-response curve, and I think it's something that might be pertinent at some point. If you guys can help me with this, I'd greatly appreciate it.

CHAIRMAN TOWBIN: Dr. McGough, would you like to answer Dr. White's question or would you like me to respond?

DR. MCGOUGH: [inaudible]

CHAIRMAN TOWBIN: I can start. So, I can't say that I'm intimately familiar with the studies that were done, the pivotal studies. Although, I think that generally they were constructed as multi-site studies that all used the diagnosis in the diagnostic and statistical manual and a standardized way of making that diagnosis. Now, of course, any study like this that's a multi-site, international study would depend on having adequate training and inter-rater agreement for the diagnoses that were made. But if you're asking the question of whether it's possible to accurately make the diagnosis of schizophrenia across cultures, races, nationalities, dialects, the answer is very much yes. And the World Health Organization and others have put a great deal of effort into doing that in order to get

accurate epidemiological assessments for the prevalence of these conditions in different nationalities.

DR. WHITE: And what about the dose-response curves that were listed in the statistical analysis that had very unusual interpretations?

CHAIRMAN TOWBIN: Well, actually there's a little bit about this in some of the other materials that we received where there is some question, as you say, we usually think about more is better, but that isn't, of course, necessarily so for every drug. And so, some of those responses may have also been a result of people dropping out of the study as they had more and more side effects, so as adherence to the regimen decreases and people leave the study. If you do last observation carried forward on those larger doses, then you're going to see those actually drop out at a greater level and you won't see efficacy, whereas those that hang in at a more moderate level may have a better outcome, if you will. They hang in for the duration of the trial and do show some benefit. But what you're looking at, I think, could be a competition between adverse effects of being on the drug and any clinical benefit that's seen at higher doses.

DR. WHITE: Dr. LaRussa, did you have a comment? Should the label reflect it, I guess, is...?

DR. KARESH: I've put on the screen a backup slide that I had made that does labeling, that does discuss dose in a little more detail that I did initially. The recommended starting dose is 3 milligrams a day. Information on dose increases, if necessary, is provided in labeling, and labeling does state that there was no clear enhancement to efficacy at the higher doses, while adverse events were dose-related.

DR. WHITE: I'm sorry; I don't think that's in the pediatric section, though, is it?

DR. KARESH: My understanding is it's Adolescent Dosing section, but I defer to the division.

MALE SPEAKER: We're checking on that.

DR. YAO: It's in -- sorry, it's in section --

DR. WHITE: It may be in the general information, but in the dosing indications for children, I don't think it's reflected. Is it? I mean -- Dr. Yao?

DR. YAO: Yeah. So, again, it's sometimes hard, tricky, to figure out where information is contained in the labeling, but under 2.1, which is the traditional section for dosing, and a specific section for adolescent dosing in 2.1, it describes about a starting dose of 3 milligrams per day, and then not to increase the dose more than every five days, and that prescribers should be mindful that in the adolescent

schizophrenia study, there was no clear enhancement to efficacy at the higher doses.

DR. WHITE: I was looking at 8.4, which --

DR. YAO: Not sure.

CHAIRMAN TOWBIN: Dr. LaRussa.

DR. LARUSSA: So one other comment about those studies that was kind of bizarre is that if you looked at the response to placebo in the under-51 versus over-51 kilos, it was dramatically different. And do you have any explanation for that?

CHAIRMAN TOWBIN: You know, that isn't all that unusual in the psychopharmacology of young children for some of these more complex conditions, where, in fact, for example, treatment of depression, you have very high rates of placebo response. And one of the problems in demonstrating drug efficacy for things like SSRIs, you may remember when we looked at those, is that it's very hard for the drug to be to placebo in order to show its efficacy, and for younger patients it's particularly a challenge.

Other comments? Questions? Dr. Wagener.

DR. WAGENER: I just want to follow up on the public comment earlier today. Did you notice any difference in gynecomastia or weight change, severe -- or adverse effects in

adolescents versus adults? I believe your comment was that they were pretty much the same, but I just wanted to make sure.

MS. SALAAM: Hi, Tracy Salaam again, from -- safety evaluator from DPV.

CHAIRMAN TOWBIN: Thank you.

MS. SALAAM: We do not actually look at adult patients in this review. We just focused on pediatric patients.

CHAIRMAN TOWBIN: I think Dr. Wagener's question is a little different, but correct me if I'm wrong, Dr. Wagener, which is, are the rates for weight gain or gynecomastia different in adolescents or children compared to adults?

DR. WAGENER: But I think that's what she answered, is that they didn't look at adults, so she can't give me a rate difference.

CHAIRMAN TOWBIN: Dr. Yao?

DR. YAO: So just as a clarification, we reviewed this over the break because of the open public session did bring up these questions, and so it's part of the Warnings and Precautions section. So it's pretty prominently placed within labeling, is this issue of metabolic changes, including weight gain. And there's a very nice table that describes weight gain in adults compared to weight gain in children. And while, as Dr. Karesh pointed out, there were no clear increases or changes in weight, it was in the patients who gained more than 7 percent

of their body weight during the study that there was a -- in adults at the highest doses I think it was 9 percent of the patients, and in children it was 18 percent of the patients. So there was --

DR. KARESH: And I do have the pediatric data that she's referring to up on the screen.

DR. YAO: Yeah, so it does -- it does look like there was maybe a higher -- or I'm not sure that you can say that. I'm just -- in terms of those data, it looks like adolescents did gain -- tend to gain more weight.

Now, as far as the gynecomastia, again, it's labeled prominently under Hyperprolactinemia in Section 5.7, and it describes many of the issues related to hyperprolactinemia, including increase in mammary tissue, gynecomastia. And it does not specifically describe a difference between adults and adolescents, so I can't answer that one here.

CHAIRMAN TOWBIN: Oh -- yes, Dr. Baker.

DR. BAKER: This is Susan Baker. I just have one question for you all, and I hope you'll help my memory. I believe it was in the 2008 briefing information you gave us that the FDA had some concern over several sites because of the data that was obtained. I just want to know that you -- and you were going to investigate those sites. I just want to know that you completed that and you were happy with your investigation and

the results were acceptable. Is that correct? I didn't see any resolution of that, just that it was pointed out it was a concern and that you were going -- you were investigating. I believe there were two sites, one in Russia and one in the Ukraine. Do I remember that correctly? Is that data acceptable?

DR. LEVIN: This is Bob Levin, Division of Psychiatry Products. The issue is resolved. I don't know the -- we can get the details about the findings, but we look at that, if we had concerns, we actually had the companies go back, remove certain sites that are suspect or problematic, and those analyses were -- ended up being positive regardless of removing those sites. But, yeah, the issue's been resolved. We felt there's no need to do anything beyond that.

DR. BAKER: So the data that was presented in the 2008 briefing included the data that was questionable. I wasn't sure in the newer stuff that that data had been expunged, if it was not good data. But it was, I guess. Okay.

CHAIRMAN TOWBIN: Are there any other comments? Dr. Mink?

DR. MCGOUGH: This is really more a question and a concern about the class of drugs in general. There's reason to be concerned, I think, particularly in the youngest group of children and in the adolescents as well, that it's not just

incidents of adverse events, but it's irreversibility of them once they are initiated. Is there any way, with the current surveillance systems, to get at that question? I mean, this is -- these are reporting individual incidences. And so if -- the concern is, if you gain 20 -- or if 20 percent of the people gain more than 7 -- increase their body weight by more than 7 percent, and there's the same incidence of hyperlipidemia seen in adults, there's some reason to think that this may be less reversible if it starts early and may be related to duration -- the reversibility may be related to duration of treatment just like tardive dyskinesia, for example. Is there any way, with the current surveillance system, to track reversibility?

DR. HAUSMAN: Ethan Hausman. With respect to the AERS reports, we have the data we get. So if they are -- if it's a longitudinal report -- some of them actually are longitudinal, and the way the AERS system works, once some reporters, some investigators, professionals, are aware of the system, they will in fact send in updates. My colleagues from DPV can support that. Some reports, we get five, 10, 15 versions of the same report as more data comes in. So there's that mechanism. But AERS, per se, is static. So we have what we have, and that's it.

In terms of other mechanisms that are in existence -- not that we have access to them -- one could postulate that, you

know, people could track this through an epidemiological study if they want, but AERS is not a mechanism where we can do that kind of analysis, because we don't always have the data.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: Is there common language in the labels for atypicals around metabolic syndrome and effects?

DR. LEVIN: Bob Levin. Yes, we have a class language for -- there's some language that it's identical class language for all antipsychotics. We have the individual data with that drug in labeling, and tables and text as well. So it's a prominent warning.

CHAIRMAN TOWBIN: All right. Well, so, if there aren't other comments or questions, I think that we're ready to address the specific question, which is whether we are recommending that this be returned to routine monitoring. And I have the sense from the group that there's a lot of concern about weight gain on this drug and this class of drugs, particularly in the pediatric population, and that we wish we had more and better data to be able to examine what becomes of children who have that kind of weight gain and whether it's related to only the time the children are on the drugs or if it may be, in fact, less reversible.

DR. ROSENTHAL: May I just expand your expression of concern to include not just weight gain but also metabolic syndrome and dyslipidemias and maybe the hyperprolactinaemia?

DR. HAUSMAN: Yeah. Anyone else?

DR. LARUSSA: I have something that --

CHAIRMAN TOWBIN: Dr. LaRussa?

DR. LARUSSA: You know, I know these are animal studies, but I think a 10 percent difference in bone density is something that needs to be looked at a little more.

CHAIRMAN TOWBIN: So I think one of the things the committee is saying is that if there could be a way for the FDA to identify a mechanism for us to learn more about the rate of these kinds of events in children, adolescents who get these drugs, the longitudinal outcome of individuals who have these kinds of ill effects, I think that the committee would very much like to know that, and I think that practitioners who now, I think, are quite aware of the concerns about metabolic syndrome and weight gain in the populations that received it. So, though they're very aware of it, I don't think anybody really has a good grasp on what becomes of those children or what steps can be taken to address that once one sees it. Dr. Santana?

DR. SANTANA: So, kind of following up on that, maybe the agency can clarify for us, if you can, in this meeting, in a public meeting, what additional studies in children are out

there that you have committed the sponsors to bring in, and what questions are going to be answered by those studies? I got a sense that there were some studies, but I don't still understand the universe of those studies and what they're trying to answer.

DR. LEVIN: Bob Levin. In general, for any indication -- for example, once a company has established efficacy for a short-term study, it's always a requirement, actually, for filing, not just for postmarketing. It's a requirement to have long-term data to submit the initial NDA. In this case, they did actually probably perhaps more than we typically require. There's been two long-term studies. And within those long-term studies, we always ask for systematic data on weight gain, lipid effects, glucose effects, insulin. So there is information available. We had that for a number of trials across various antipsychotics.

DR. SANTANA: But are those studies ongoing, is what I'm getting at. I don't understand what -- tell me when those studies are going to be done, or if they're going -- longitudinal, when is the -- when is the timetable?

DR. LEVIN: Yeah, for this -- in this case, for paliperidone, we do have the data in-house very recently, and we're reviewing the long-term data. And we -- there's a very detailed analysis we requested and the sponsors agreed to

regarding all these -- especially the metabolic abnormalities. It's a great area of concern for us too.

DR. SANTANA: So there are -- there are either ongoing studies that you have the data, or are there plans for additional studies?

DR. LEVIN: On -- well, actually completed. For this drug, they recently completed the long-term studies, two long-term studies.

CHAIRMAN TOWBIN: Dr. Cnaan?

DR. CNAAN: On the same issue, it's not just the rates of these various events that were mentioned, but I'd really like to see some data on exposure, because a 7 percent weight gain in six weeks -- well, what happens at eight months? So, by exposure, by gender, and by age. I have no sense if this looks the same in the 8-year-old than in the 14-year-old. So with this wonderful data that you now have in-house, I would be interested in seeing more. We don't have enough, in my sense.

CHAIRMAN TOWBIN: Dr. Reed.

DR. REED: That was what I was going to say, actually, and to the psychiatrist FDA officer -- I'm sorry; I didn't get your name -- but do you have a sense of when that in-house data, now that you have a wealth of information there, will sort of be analyzed? And can we assume that that will be brought back when performed to our committee?

DR. LEVIN: Yes. Yeah, we're working on it currently. We plan to -- I can't give an exact timeline, but it's a high concern on our list of things to do.

DR. REED: So it is a priority?

DR. LEVIN: Yes, it is.

DR. REED: Thank you.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: So just to continue to beat on this point, so we've -- we have new data, but can you help us understand the kinds of questions that this -- that these new data points will help us to answer? What specific aspects of the relationship between exposure to atypicals and these -- call them cardiovascular risk factors and risk factors for gynecomastia and these other endpoints? What specific relationships between those might be answered by the data that are now in hand?

DR. LEVIN: Specifically for correlating laboratory data or weight data with clinical adverse events? Is that -- I mean -- or just in general, what are the plans for analysis?

DR. ROSENTHAL: Well, I'm -- you know, I'm trying to understand what questions. It -- we all -- sometimes I'm -- we on this committee over the years have so frequently been data-starved that when we hear that data exists, we feel like that's a reasonable endpoint, just that we've got data. So I guess

what I'm asking you is for the next -- for the sort of next layer of understanding. What kinds of questions might we be able to address with the data in hand?

DR. LEVIN: Sure. Yeah, we'll address exactly the kind of questions that are raised; for example, metabolic changes including weight, lipids, and glucose by time, duration of exposure. We'll do analyses based on baseline body weight, weight -- subgroup weight categories. We'll look at male and female, potential differences. All the questions that have been raised here, we will look at as part of -- as sort of a standard part of our review of metabolic data.

CHAIRMAN TOWBIN: And that would be stratified by age?

DR. LEVIN: Yes.

CHAIRMAN TOWBIN: Dr. McGough.

DR. MCGOUGH: I think the real data gap is -- I don't know how long your long-term study was, if it was a two-year study or a three-year study, but I think the biggest question of concern is the long-range consequences. I didn't really understand when you said that the sexual maturity of the female dogs was seemingly permanently stopped. I didn't know what that meant. Were they prepubertal forever, or -- but I think the question is, for kids with metabolic syndrome or, those other effects, you know, five years down the road or 10 years down the road, are there consequences? And I don't know that a data

set like you have would get at that, and I don't really know how we would get at that, but that really is the key question. These are bone density issues, the metabolic issues. You know, what's the consequence by the time they've reached puberty or even adulthood?

DR. LEVIN: Exactly. Right. There's obviously limitations to the one- or two-year study. Within the two-year study, they do -- they do counter-staging, they evaluate development throughout the study, but what you're saying, obviously it's not enough to look at those other serious outcomes, so there are ways to do that. We don't have the easy answers, but it would require looking carefully at what kinds of designs of epidemiological studies one could do, and how to best assess that.

DR. MCGOUGH: If I could just follow up, I think really the question is not so much what are -- I think we kind of know the effects while you're on the drug. Clinicians see that. But what are the long-term developmental consequences for a period of exposure down the road? I think that's the real kind of theoretical thing to be grasped.

ROBERT NELSON: Right. Sure.

CHAIRMAN TOWBIN: Dr. Nelson?

DR. NELSON: Yeah, just one opportunity for you to clarify, and then I'm going to give an opportunity for Dr. Cope

to comment on the problems with epidemiologic studies. But what's the lower age limit of the data that you've got in? I don't want people to get unreasonable expectations about how far down you can go into the off-label use.

DR. LEVIN: Yeah, we're really sticking by the on-label use of controlled studies. So it would be for this -- in this case, it would be the ages 12 to 17.

DR. NELSON: Right. So I just want to make sure we're not going to answer the 8-year-old. I mean, that's why I wanted to get that on the record. And long-term, obviously, in our parlance is two years, in this case.

DR. LEVIN: Right.

DR. NELSON: So, and maybe Dr. Cope -- after the 2008 meeting, there was attempts to try and get the long-term epidemiologic data, but I'd like her to just comment on why that was a problem.

CHAIRMAN TOWBIN: Thank you.

DR. COPE: I just wanted to remind many of you that we had a PAC meeting in September of 2011, and at that time they were presenting some of the data from AHRQ and all of that. So some of our tries, some of our really looking to get epidemiological data, it has a lot of codes, but when we went in there, they weren't necessarily coming up with reliable weights, and then you don't usually have the Tanner-stage puberty, and

then of course the boys and girls are entering and prolonging in different times. So, I mean, we are up for any epidemiological ideas that people have on good databases, because -- especially when you want to compare across the different groups of atypical antipsychotics and kids switching and all of that. But when we presented the data about the AHRQ, that was very fascinating, but it didn't have the reliable weights, which was one thing. It did have lab, you know, data on lipids, maybe, and that, but it's really hard to get a reliable database that we'll follow long-term, so we are up for ideas and recommendations.

CHAIRMAN TOWBIN: Well, there may be a mechanism to think about funding what would be a prospective study of individuals who have developed weight gain above 7 percent of their body weight on these drugs and to follow them over a period of time. You might get a potpourri, and indeed you might see people on combinations of atypical antipsychotics rather than on just one, but there still might be some value in looking at what some of their metabolic parameters would do over a two- to three-year period for a longitudinal study and would be ahead of some of what we've got already. Were there other comments, then, before we vote? Ms. Celento.

MS. CELENTO: Amy Celento. Just quickly, along those lines, I mean, childhood and adolescent obesity and obviously adult obesity are some of the biggest health issues going, and,

you know, I think you have to look for the opportunities of what studies are already being done, being funded. What are the hot public health issues, and how can you tag that, you know? Can this be a subcategory of a study that's already being planned, just looking at childhood obesity and following those people? So I really think that you have to look for bigger opportunities here, because we can't say 2008, 2011, 2013. We can't sit here in 2015 and just say, "Oh, we really don't have good data. We don't have a long-term study. We didn't have good weights." You know, there's -- there are ways to capture this, and I think you have to look bigger.

CHAIRMAN TOWBIN: Thank you. Well, so I think we do need to return to the question. The FDA is looking to us to learn whether we want to return this to routine monitoring, and so I'd like to call for a vote. There are no other comments. So, Dr. Cnaan, can we start with you?

DR. CNAAN: So, on this one I disagree with routine monitoring. I'd like for us to see the analyses of the recently obtained data from the sponsor according to the parameters stated in the discussion. I would like to see a little bit of a better breakdown of the drug utilization data, because that would not give us any of the adverse events, but it would give us how to relate the sponsor data to what actually happens out there in some coherent way, and I strongly support what Amy

Celento said. There are a ton of metabolic studies going out on there unrelated to this issue, but for sure some of them -- and I'm not familiar with those studies closely -- but some of them gather what are the concomitant medications that these children are on. So I don't know what the path is, but there ought to be a path to get at these data these days, given the national attention on these issues.

CHAIRMAN TOWBIN: Dr. Nelson?

DR. NELSON: Just a comment that was made previously on one of the other products where the complexity of this issue, you could concur to routine monitoring, recognizing the fact that our routine monitoring in a passive database, so on and so forth, is limited. Routine monitoring does include feedback to the committee based on the data that's come in, and of course, FDA would love to be able to partner with people that could fund prospective studies of these issues such as maybe the extramural program at NIMH. You know, so I think what I'm suggesting is routine monitoring is one thing, and then the need for these other data sets, which we're aware of, is another thing. So I would just ask you as you go through to sort of divide the question so it's sort of clear that you could concur with routine monitoring and still say you want to have all these other activities.

CHAIRMAN TOWBIN: So, Dr. Cnaan, does that alter your comment?

DR. CNAAN: So that returns me to my first question of the day, actually, of what does routine monitoring -- if you define for me in a way that I could say, "Sure, I agree, but I'm happy to do so."

DR. NELSON: Okay. Well, maybe -- Ethan, do you want to define that?

DR. HAUSMAN: Ethan Hausman. Routine monitoring for pharmacovigilance includes having drug portfolios by specific drug and by drug groups that are routinely, as in continually and continuously, looked at at a periodic basis by the safety evaluators, and we employ mechanisms such as data mining. It's not we close the book on a drug and open it up a year later when we get ready for the advisory committee. So there's ongoing portfolio monitoring. And if signals come up, we work them up to see if there's new signal with reasonable quality data. If there's something in the background that might be lower in priority in the label but we notice a big rush of reports, to use a sloppy phrase, we can work that up as well. So, while the reports are received in a passive capacity, we actively monitor the data system on a regular basis.

CHAIRMAN TOWBIN: I think what they're saying is that it's possible to have routine monitoring and for the kind of study that you're requesting to be available. Dr. LaRussa.

DR. LARUSSA: So let me ask the converse of that question. If we return to routine monitoring, what will not happen that's happening now?

DR. HAUSMAN: I -- Ethan Hausman. I have to ask you what you mean by that --

[laughter]

-- because I'm not sure of your question.

DR. LARUSSA: So you say, "FDA returns to routine monitoring." That implies to me that if we do that, you're not going to do something that you're doing now.

DR. HAUSMAN: A very brief response before I hand over to Dr. Nelson. The only thing that's different from routine monitoring versus today is, today we actually went through and generated a specific kind of report for the committee, this Pediatric Advisory Committee. But the exercises that Dr. Salaam and the other safety evaluators go through, they regularly go through and look at reports and see if there are new signals that are popping up on a very frequent basis.

CHAIRMAN TOWBIN: Dr. Baker?

DR. BAKER: This is Susan Baker. I have a lot of concerns. I went through this briefing material twice, and I

was really a little concerned about it. Your routine monitoring is passive. You are going to actively monitor a passive system, which is not -- which leaves a lot of holes, I think. Would it be out of line for me to suggest that you all consider asking this pharmaceutical company to do the same thing that you did to another pharmaceutical company with a biologic, where they are required in their postmarketing work to have an active surveillance program where they must enroll people and they're following those people for 20 years? Is that not -- is this stuff not of a big enough concern that we would want to do that?

DR. LEVIN: Bob Levin, Psychiatry Products. One thing you might be referring to is a registry. We definitely do have drugs that are approved that have such great safety concerns that we really -- we couldn't do anything about that. We really want to know for every patient who's exposed to that drug, what's the outcome? And you know, looking at specific outcomes. Probably in this case -- could I -- maybe I'll step back a little bit, actually.

About the metabolic issues and hyperprolactinemia, we also are extremely concerned about the effects both, you know, the symptoms, the levels themselves, the weight gain, plus, more importantly, of course, the long-term effects. We absolutely think it's an important area. We already did it. We know these things are drug-related, or dose related. They're clearly dose-

related. They're clearly duration-related. So we have a great level of concern.

There -- we could design studies. We would have to consider looking at, you know, very well-designed, thorough epidemiological studies to answer a specific question. It would have to be studies designed. The only -- the best way we could use epidemiological data is to really design prospective studies. It's often hard to look at studies designed for another purpose and cull out, you know, the facts that might be -- the data obtained during that course of the study but not really have it been designed that way.

So we ask ourselves every day these questions. What's our level of concern? What can we do about it? Can we, you know, improve labeling, look for other studies? It's an excellent point. To what level -- what level of concern must you have for a certain drug to actually have a patient registry and really, ideally, follow every person who's been exposed to that drug? In this case, it was difficult to do. We don't -- while there's tremendous safety concerns, it's probably not practical or reasonable to have that extreme of an approach, to have a registry.

CHAIRMAN TOWBIN: Dr. Nelson, and then Dr. Hausman.

DR. NELSON: I'm going to make, with permission here, two suggestions. There's the data that you've heard about

that's in-house that's not yet analyzed. And so, to some extent, the kinds of questions one would want to ask downstream of that data are yet to be defined, what kind of questions are answered on that data yet to be defined. So one suggestion about what you might want to consider recommending [laughs] is that at the time that that analysis is conducted that, in fact, there be an opportunity to feed back what we can -- what we have learned from that data, and then have a discussion about what more needs to be done at that point.

I don't know the answer to that. But that is a different question than routine monitoring, because I think all of us recognize the weaknesses of active monitoring of a passive system, which is why the FDA is investing in Sentinel and Mini-Sentinel and other activities. So routine monitoring versus that other activity, that's why I suggest they're really two separate issues.

CHAIRMAN TOWBIN: Dr. Hausman.

DR. HAUSMAN: Dr. Nelson actually addressed what I was going to say.

CHAIRMAN TOWBIN: Dr. Baker, you wanted to respond.

DR. BAKER: Yeah, this is Susan Baker again, and I'm respectfully asking a question because I could be wrong with this. But what I understood from one of your answers to another member of the committee was that the data that you have in-house

is not strong in terms of weight. Is that correct? That the weight -- this is our primary end point, and so you wouldn't be able to give us BMIZ scores or anything like that. Maybe -- perhaps I misheard; I'd love to be corrected.

DR. NELSON: Dr. Cope was referring to an epidemiologic study that was done out of Rutgers where the sampling of existing hospital databases in an attempt to do an epidemiology study did not have accurate weights to where you could begin to draw those conclusions; nothing to do with this database.

DR. BAKER: You do have good weights and BMIZ scores.

DR. NELSON: Well, I mean I'm not sure what they can say about the data, but it --

DR. NELSON: What she said had nothing to do with that data.

DR. BAKER: But if you don't have good weights, then what's the point in weighting for your study? I -- that's just that I'm respectfully answering, because this is our primary outcome, the thing that we're all so concerned about.

DR. HAUSMAN: Yes, in these study -- in the case of this antipsychotic and as with others, and actually throughout all programs for psychiatric drugs, we do get good data. We get prospective data on weight, BMI, height, assess --

CHAIRMAN TOWBIN: So I understand your answer is for the data that you have that information does contain good weight data.

DR. HAUSMAN: Yeah, it does. It has the right --

CHAIRMAN TOWBIN: Thank you.

DR. HAUSMAN: -- and the companies do the right analysis for us as well. They take the data and look at T-scores and all those parameters.

CHAIRMAN TOWBIN: Dr. Mink.

DR. MINK: Unfortunately I have to leave for the airport, but I wanted to say that regardless of what happens with routine monitoring, I want to hear back from the FDA about these questions with the results of those data. Even if those data turn out to be not concerning, I want to hear back from the committee, and I'm particularly concerned about the youngest age group too. There may be no new safety signals there, but it may be that there is increasing weight or increasing strength of the existing safety signal. So I would -- my vote would be to have a report back to the committee in, let's say, two years with an update. And if there's anything that emerge from the data that have just been received in-house that is more concerning, I'd like to hear back sooner.

CHAIRMAN TOWBIN: Very well. So if I understand correctly you want to hear back in two years related to the class or this particular agent, Dr. Mink?

DR. MINK: Well, that's a very good question since this is a relatively small component of the class, and it's really a class concern. But the way it comes to the committee typically is drug by drug. So whatever -- you know, whatever works, but I want to hear back.

CHAIRMAN TOWBIN: Very well. So, before you leave, I guess what you're saying is that routine monitoring plus is what you're -- good.

Dr. Cnaan would you like to now let us know how you think about this?

DR. CNAAN: Yes, let me amend the statement to routine monitoring, plus my previous suggestions of analyzing the study that is in-house, juxtaposing it with the concurrent drug utilizations so that we have a context, since we are looking right now at 17,000 prescriptions off label in the younger age -- not prescriptions, patients -- and 120,000 prescriptions in the younger age. So I want to see that. And the third piece of this would be the active monitoring of the passive reporting, because that might be a place where one can pick up these weight gains or other problems in the younger age group that the sponsor's data won't have.

CHAIRMAN TOWBIN: Dr. Reed, I think we're up to you.

Dr. Wagener. I'm so sorry.

DR. WAGENER: Can I just make a suggestion?

CHAIRMAN TOWBIN: Sure.

DR. WAGENER: Because we're going to get to the end and we're going to have 43 different options from 13 different people.

CHAIRMAN TOWBIN: [affirmative]

DR. WAGENER: And can we make -- as I understand it, they have an in-house data set that's a continuation of randomized control trials. So that's going to be a very set, very small, specific. That'll give two-year data. Two is we have the standard FDA monitoring that's available, which normally would bring a report back with a change in the labeling or in three to five years. So I would suggest we make one motion that says we answer the first question, we get the data back in a year, 18 months from now from this study that they are analyzing, and then have a second vote, and that is we approve routine monitoring, recognizing that when we get that first data back, if people say, "Now I want to know more information about off-label use or whatever," that initiates a whole other process, very potentially expensive and maybe sequestered, that would be addressed at that time. We cannot make that recommendation at this time, as I see.

CHAIRMAN TOWBIN: I think that's what Dr. Nelson was saying. So --

DR. WAGENER: So I would propose --

CHAIRMAN TOWBIN: Please do.

DR. WAGENER: If you'll accept a motion, I would move --

CHAIRMAN TOWBIN: I do.

DR. WAGENER: -- that for the in-house data set that's available, as soon as that is evaluated, a report come back to this committee with the information related to that data set.

CHAIRMAN TOWBIN: Very well. So I guess what we need to -- Dr. Hudak, do you have a comment to make about this?

DR. HUDAK: I just would like to maybe put out a couple possibilities for how some information might be obtained in a more longitudinal fashion and whether it's appropriate to ask the FDA to explore these opportunities. So one would be, you know, talking to the Pediatric Primary Care Trial Network and see if there is a way to pull data on children within practices, all the children on risperidone or this other, Invega, and sort of see what happens over time.

And the other is, you know, this is the year of managed care. I mean, there are, you know, large Medicaid managed care organizations where these kids tend to concentrate that can have all of this information from their databases.

CHAIRMAN TOWBIN: Well I want to rein this in a little bit because we have a motion on the table. So --

[talking simultaneously]

Please do Dr. Santana.

[talking simultaneously]

DR. SANTANA: Let me see if I understood what you said, Dr. Wagener. You're saying is that we're voting on a recommendation today of what we want to see when this data gets analyzed and defer until that point the recommendation about going back to routine monitoring. Is that what you were saying?

DR. WAGENER: My motion is just the first, is that we want to hear back. Now, what the committee decides to do about the routine monitoring, I feel, is the second question.

DR. SANTANA: Okay.

CHAIRMAN TOWBIN: Great. So let's quickly take a vote on the motion before us that was put by Dr. Wagener about whether we would like to see this data back to the committee as soon as the analysis is complete. So, Ms. Celento, do you mind starting us out?

MS. CELENTO: I second that motion. I concur with that motion [laughs].

DR. WIEFLING: Bridgette Wiefeling. I concur.

DR. WAGENER: Jeff Wagener. I agree.

DR. GLASIER: Charles Glasier. I agree.

DR. FRANCO: Israel Franco. I agree.

DR. DRACKER: Bob Dracker. I agree.

DR. LARUSSA: Phil LaRussa. I agree.

DR. CATALETTO: Mary Cataletto. I agree.

DR. HUDAK: Mark Hudak. That's easy; I agree.

DR. BAKER: Susan Baker. I agree.

DR. WHITE: Michael White. I agree.

DR. ROSENTHAL: Rosenthal. Agree.

DR. MCGOUGH: Jim McGough. Agree.

DR. SANTANA: Victor Santana. I agree.

DR. REED: Michael Reed. I agree.

DR. MINK: John Mink. I agree.

DR. CNAAN: Avital Cnaan. I agree.

CHAIRMAN TOWBIN: Good, now we can vote on the issue about routine monitoring, and I'm getting lots of motions. So -
- Dr. Cnaan.

DR. CNAAN: For the routine monitoring, I agree.

DR. MINK: John Mink. Yes.

DR. REED: Michael Reed. I agree.

DR. SANTANA: Victor Santana. I agree.

DR. MCGOUGH: Jim McGough. I agree.

MALE SPEAKER: I agree.

DR. WHITE: Michael White. I agree.

DR. BAKER: Baker. I agree.

DR. HUDAK: Mark Hudak. I agree.

DR. CATALETTO: Cataletto. I agree.

DR. LARUSSA: LaRussa. I agree.

CHAIRMAN TOWBIN: Dr. Dracker?

DR. DRACKER: Bob Dracker. I agree.

DR. FRANCO: Israel Franco. I agree.

DR. GLASIER: Charles Glasier. I agree.

DR. WAGENER: Jeff Wagener. I agree.

DR. WIEFLING: Bridgette Wiefling. I agree.

AMY CELENTO: Amy Celento. I agree.

CHAIRMAN TOWBIN: Thank you very much for helping us out with that. Dr. Ellenberg.

DR. ELLENBERG: Yeah, just real quickly before we move into the next phase of the discussion, for anybody who has to leave to catch a flight, please make sure that you turn in your CDs, either to me or to Sheila out at the desk. If you have any questions on your flight, you can speak with Eunica [spelled phonetically]. Thanks a lot.

CHAIRMAN TOWBIN: All right. Dr. Hausman, I think that you wanted to make an announcement.

DR. HAUSMAN: Yeah, Ethan Hausman. I just wanted to let everybody on the PAC know this is going to be my last PAC meeting. I'm transferring from the Office of Surveillance and

Epidemiology over to Pediatric Maternal Health staff with Dr. Yao.

DR. HAUSMAN: So I'll still be working with the PAC but in a slightly different capacity.

INFORMATIONAL UPDATE -- PHARMACOGENETICS OF CODEINE

CHAIRMAN TOWBIN: Thank you for that Dr. Hausman. Okay. So now I think we're ready for our next speaker. Let's see. I've got my -- so this is Dr. Muguleta --

DR. MULUGETA: Yeah.

CHAIRMAN TOWBIN: -- who received her undergraduate degree in pharmacy and her doctorate in pharmacy from the University of Kentucky and completed a two-year residency in clinical pharmacy with a focus in pediatrics at Inova Fairfax Hospital in Falls Church, Virginia. Following her residency, Dr. Muguleta practiced as a clinical pharmacist in the University of Virginia Medical Center, and then joined Children's National Medical Center in Washington, D.C., as a critical care specialist. And later as director of clinical services. Her primary research area was sedation management of pediatric patients supported on mechanical ventilation.

She has been a faculty member at -- in the Department of Pediatrics at the George Washington University School of Medicine, in the Departments of Pharmacy at the University of Maryland College of Pharmacy, and Howard University School of Pharmacy. During her eight years of service at Connecticut Mental -- I'm sorry [laughs] at the Children's National Medical Center, Dr. Muguleta chaired several committees, including Pharmacy and Therapeutics and Coagulation Task Force and

Antimicrobial Committee. She also served on the IRB there. In 2008 she joined the Office of Clinical Pharmacology at the FDA as a clinical pharmacologist in the Pediatric Group. And she serves as a representative for OCP on the Pediatric Review Committee.

DR. ELLENBERG: Hi, this is Walter Ellenberg. One more time, I just want to make a comment before we get underway and moving ahead. This particular talk is just a briefing to the committee. It's not one where we're going to sit and go back and forth and ask questions. It's just to get an update --

[laughter]

-- from her -- that's the intent of this. It's just a briefing to the committee. I just want to make sure you all understood that.

[laughter]

DR. MULUGETA: Okay. Thank you.

CHAIRMAN TOWBIN: Thank you, Dr. Muguleta.

DR. MULUGETA: So, over the next 10 minutes or so, I'll give you an overview of the pharmacogenetics of codeine. First I'll start by talking about the general pharmacology of codeine. Codeine is a naturally occurring opioid alkaloid. It's demethylated to morphine for its analgesic activity. Therefore, it's often referred to as a pro-drug. It's used for relief of mild to moderately severe pain. In children the usual

dose is 0.5 milligram per kilo every four to six hours. In adults the dose ranges from 15 to 60 milligrams. In combination with Acetaminophen it's approved in children 3 years and older. It also has antitussive effect, and therefore it's commonly used in cough and cold products.

The side effect profile of codeine is broadly similar to that of other opioids. It includes CNS adverse events such as drowsiness, dizziness, and sedation, as well as GI adverse events, so nausea, vomiting, constipation. At higher doses codeine has some of the disadvantages that morphine has, including respiratory depression.

The vast majority of the PK data for codeine is based on adult data. So, following oral administration, codeine is readily absorbed from the GI tract. It does cross the blood-brain barrier, and it is excreted in breast milk. Its metabolism is primarily Hepatic through glucuronidation and demethylation through CYP3A4 and CYP2D6. About 10 percent of the parent drug and its metabolites are renally excreted.

This depicts the metabolism of morphine -- of codeine. Approximately 80 percent of an administered dose is converted to inactive metabolites, Norcodeine and codeine-6-glucuronide. The demethylation of codeine to morphine is a minor pathway, and it accounts for about 5 to 15 percent of the clearance of codeine in most patients. However, since morphine is the active

component of codeine, the analgesic activity of codeine then depends on the CYP2D6 activity.

CYP2D6 is involved in the metabolism of approximately 25 percent of drugs. It's a highly polymorphic enzyme. More than 80 CYP2D6 allelic variants have been identified. CYP2D6 alleles are characterized as wild-type, which is normal function, reduced function, or non-functional based on the expected level of activity.

Patient's phenotype classification is also based on expected CYP2D6 activity. And that can range from complete deficiency in poor metabolizers to substantially higher than average activity in ultra-rapid metabolizers.

The extensive metabolizer phenotype represents normal activity for CYP2D6. However, there could also be intermediate metabolizer phenotype with reduced activity. For the purposes of clinical trials, intermediate metabolizer phenotype and extensive metabolizers are collectively referred to as extensive metabolizers.

In the table you can see that various prevalence for the -- depending on the phenotype. The estimated frequency FPMs is about 10 percent and 1 to 2 percent for ultra-rapid metabolizers. However, the table is based on the prevalence in Caucasian population, and they -- that may significantly defer based on ethnicity and race.

This table provides the prevalence based on ethnicity and different populations for the ultra-rapid metabolizer phenotype. And I -- as you can see, there is a wide range of prevalence, 1 to 2 percent in Northern Europeans and Asians, up to as high as 30 percent in Africans north -- in Ethiopians as well as some Arab populations.

So, as I mentioned previously, CYP2D6 does control the analgesic effect of codeine, and CYP2D6 polymorphism can alter drug exposure. This is the concentration time curve for codeine and its two active metabolites, morphine and morphine-6-glucuronide. And this is following a single dose of 30 milligrams in EMs, which are denoted with a blue line, ultra-rapid metabolizers, or UM with a red line, as well as poor metabolizers, or PMs with the green line. And if we can focus on the concentration time profile for morphine and morphine-6-glucuronide, you can see that exposure in ultra-rapid metabolizers, again the red line, is about 1.5 fold higher compared to exposures in EMs, which are the blue line. And the same thing is observed for morphine and morphine-6-glucuronide.

Another observation that's worthwhile making is that exposure in poor metabolizers for morphine and morphine-6-glucuronide are at lower limit of quantification. So this suggests that there is increased conversion of codeine to morphine in ultra-rapid metabolizers, which increases the risk

of codeine toxicity in 1 to 2 percent of patients. In addition, about 5 to 10 percent of patients who are poor metabolizers will have ineffective analgesia following codeine administration.

In the same study, patient's phenotype was determined using a typical phenotyping substance, in this case Metoprolol. And if you look at the blue lines, which are Ems, and the red dots, which are ultra-rapid metabolizers, or UMs, there is -- the morphine concentration is really highly variable within those two groups. In addition, there is a subgroup of EMs who are able to metabolize codeine to morphine at the faster rate, similar to UMs.

Several studies have documented the lack of analgesic effect in poor metabolizers. There are case reports of morphine toxicity in breastfed infants of ultra-rapid mothers, and this has led for -- to a change in the product label to include this as a warning. In addition, there is a case report of morphine toxicity in an adult patient who is an ultra-rapid metabolizer who is also taking a CYP3A4 inhibitor. There are several cases of reports of severe or life threatening side effects in pediatric patients who were ultra-rapid metabolizers, and those cases will be described in the next presentation by Dr. Racoosin.

It's important to note that other opiates such as Tramadol, Hydrocodone, Oxycodone are also metabolized at least

in part by CYP2D6. And this table nicely breaks down the pathways of CYP2D6, what percent of the drug is metabolized through that pathway, which metabolites are active, and whether the parent or metabolite contributes to the analgesic effect of the drug.

So for Hydrocodone approximately 14 percent of Hydrocodone is converted to Hydromorphone via CYP2D6. So, following Hydrocodone administration, we have data to show that poor metabolizers will have levels about five times lower than extensive metabolizers. However, the difference between Hydrocodone and codeine, the parent does contribute significantly to the analgesic effect of the drug. There is, unfortunately, no data on the PK of Hydrocodone in ultra-rapid metabolizers.

For Oxycodone approximately 11 percent of the drug is converted to Oxymorphone via CYP2D6. Fortunately, Oxymorphone is present in very low concentration in the plasma, and therefore the analgesic effect of the -- of Oxycodone is primarily due to the parent drug.

Tramadol is also extensively metabolized by CYP2D6 to O-Desmethyltramadol, which is primarily responsible for its opioid receptor mediated analgesia. Poor metabolizers have shown to have lower exposure of this active metabolite and, therefore, often fail to exhibit any analgesic effect from

Tramadol. There is also data showing that there is high exposure of this active metabolite in patients who are ultra-rapid metabolizers.

It's also important to note, just similar to codeine, Hydrocodone, Oxycodone, and Tramadol are also substrate of CYP3A4 which makes them likely to have drug-drug interactions.

So, in summary, following administration of recommended doses of codeine ultra-rapid metabolizers have an increased risk of having morphine toxicity. Poor metabolizers are unlikely to have any analgesic effect following codeine administration. Although the prevalence of UMs is low in the Caucasian population, which was around 1 to 2 percent of the Caucasian population, it can be very high in some other populations. Thank you.

CHAIRMAN TOWBIN: Thank you very much for a concise and clear presentation.

DR. MULUGETA: Thank you.

CHAIRMAN TOWBIN: Dr. Santana.

DR. SANTANA: So on slide -- well the slide where you gave us the table of the rates of genetic polymorphisms that vary by race and ethnicity --

DR. MULUGETA: [affirmative]

DR. SANTANA: -- is that data being derived from clinical trials? Because it's my understanding that most of

these polymorphisms are genotyped in research labs. Or is there -- this data coming from companies that do this and the data is validated and therefore these are correct rates?

DR. MULUGETA: I will refer this to maybe Judy Racoosin since this was an FDA safety communication.

DR. RACOOSIN: These are generally small studies that have been done in specific populations to look at the distribution of the various different polymorphisms of CYP2D6. So this isn't coming from a development program, if that's what you're asking. I --

DR. SANTANA: Are commercial labs that do this?

DR. RACOOSIN: Pardon?

DR. SANTANA: Are there commercial labs that do this?

DR. MULUGETA: Yes.

DR. RACOOSIN: Oh, yeah, you can -- I mean you can order this for a patient, or, I mean, these are -- there are commercially available genotyping tests for CYP2D6. And I would refer you to -- we've had two drug safety communications about this issue, one of which was in August of last year, and that has all of the references --

DR. SANTANA: Right.

DR. RACOOSIN: -- for these various -- all of the percentages that are on this slide. And I can send that to the pediatric team so they can distribute that.

DEATH AND RESPIRATORY ARREST RELATED TO ULTRA-RAPID METABOLISM
OF CODEINE TO MORPHINE

CHAIRMAN TOWBIN: Thank you, Dr. Racoosin. Other questions or comments? So thank you very much, Dr. Muguleta.

So I think, Dr. Racoosin, we're going to hear from you next. Dr. Racoosin has worked on premarket and postmarket safety issues in the FDA Center for Drug Evaluation Research for more than 16 years. Most recently she joined CDER's Division of Anesthesia, Analgesia, and Addiction Products as the deputy director for safety in September 2011. In that role she's responsible for managing the postmarket safety issues for the division. She graduated magna cum laude from the University of Maryland School of Medicine and completed a residency in internal medicine at the University of Chicago Hospitals. Following residency, she earned a master's in public health from the University of Illinois at Chicago School of Public Health. She is board certified in clinical pharmacology.

Thank you for joining us, Dr. Racoosin.

DR. RACOOSIN: Thank you for having me. So Dr. Muguleta laid the groundwork here for what I'm going to talk about over the next few minutes, and that's the death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine, particularly with attention to children.

Dr. Muguleta also mentioned the fact that there is labeling and has -- there's been a risk that's been identified in breastfeeding children when their mothers have been ultra-rapid metabolizers of codeine. And the case report came out of Dr. Koren's group from the Hospital for Sick Children in Toronto sometime around 2006, and FDA followed that up with a press release and public health advisory and adding labeling to the codeine containing products to describe this risk. So this is not the first time that we've dealt with the adverse effects of polymorphic metabolism of codeine.

Before I go on, I'll just say that in April of last year in the Journal of Pediatrics, there was a case series describing three children who died after getting codeine for post-operative pain management after adenotonsillectomy. And that case series led our group to evaluate this issue by doing a literature review and review of the adverse event reporting system in collaboration with our colleagues in the Office of Surveillance and Epidemiology.

I'm going to present the cases as they happened chronologically, but as I said, it was the case series from last April that tipped us off that this could be an important problem to look at. So there are four articles that describe seven pediatric patients who experienced codeine overdose and/or death and actually reported the CYP2D6 metabolizer status.

These seven cases were also identified in the search of the Adverse Event Reporting System. The first one was published in 2007 in *Pediatric Anesthesia* and described a 29-month-old child of North African descent who received combination codeine Acetaminophen after adenotonsillectomy for recurrent tonsillitis and mild to moderate sleep apnea. The child was found unresponsive on the evening of post-op day one and was able to be resuscitated. His -- I believe it's a boy -- his genotype was on the border of being EM and UM.

Subsequently there was a case published in *New England Journal* as a letter. This was from the group at Hospital for Sick Children, and that described a 2-year-old who had received a combination codeine Acetaminophen after adenotonsillectomy for obstructive sleep apnea. The child died on post-operative day two and was an ultra-rapid metabolizer by genotype.

This -- Kelly, et al, is the case series that I mentioned. This also comes from the Koren group as well as other colleagues. In fact, I believe in order to -- two of the cases are Canadian and one is from the U.S., and I think they wanted to make sure that it wasn't believed to be just a Canadian phenomenon. So this described a 4-year-old boy who received codeine post-adenotonsillectomy for obstructive sleep apnea and recurrent tonsillitis. The child died on post-operative day two and was an ultra-rapid metabolizer by

genotype. The second case was a 5-year-old boy who received combination codeine Acetaminophen post-adenotonsillectomy for a recurrent tonsillitis and snoring. The child died on post-op day one. He was considered to be a likely ultra-rapid metabolizer because of high blood morphine concentration relative to codeine on postmortem testing.

And then the third case was a 3-year-old girl of Middle Eastern descent who received combination codeine Acetaminophen post-adenotonsillectomy for obstructive sleep apnea, who was found unresponsive on post-operative day two and was able to be resuscitated at the hospital. She was an EM by genotype, but her morphine level was consistent with the UM phenotype, and I think from what Dr. Muguleta showed on her slides about the overlap in the morphine levels between EMs and UMs, this can -- has certainly been observed.

The other publication was in the European Journal of Pediatrics in 2008, and it described 3-year-old twins who had received codeine drops for cough once daily for six days. One of the twins died, and the second twin was found apneac and was able to be resuscitated. These two children were EM by genotype. There was a concern about how much dose they were getting because of the formulation being a drop formulation, and the paper described a specific analysis of the size of the drops, and it did suggest the possibility that the children had

been inadvertently overdosed. What was notable about this case is that it was a much longer time to event than the other cases I described.

So, in addition to looking at codeine, we also looked at other opioids that are commonly given to children to try and understand whether this is a finding specific to codeine or whether there are other drugs involved, because also, as you've just heard, other -- the Oxycodone and Hydrocodone and Tramadol are also metabolized in part by CYP2D6.

So there was only one case in the literature that was identified, and this was in Pediatrics in 2010, and it was a 6-year-old who had been prescribed combination -- oh, I'm sorry -- single agent Hydrocodone and Clarithromycin for a cold and ear infection. She was found unresponsive on day two and had inadvertently received two times the prescribed dose in 24 hours, and she ultimately died. There was little to no detectable CYP2D6 activity, so she was a poor metabolizer. And she also was taking Clarithromycin, which is an inhibitor of CYP3A4 so on this slide -- I just hit the wrong button. There we go. Yeah. So -- maybe it would be easier to the -- nope that didn't help. It's late in the day.

DR. RACOOSIN: So she had a lethal level of Hydrocodone. She was a poor metabolizer of CYP2D6, so nothing was going down this pathway. She was on a CYP3A4 inhibitor, and

she also was on Valproic acid, which inhibits another enzyme further down the path. So, in this case, she essentially had no way to metabolize the Hydrocodone. And this is very distinctive from what we've seen in the other cases I described with codeine where we're talking about ultra-rapid metabolizers that are generating high levels of morphine. In this case, this was a poor metabolizer. So we are -- included this for -- in the discussion for completeness, but it really doesn't relate to our concerns about ultra-rapid metabolizers.

Moving on to the AERS data, as I mentioned, the seven liniature cases that I discussed previously were all reported in AERS, and those were the only cases that actually included any kind of CYP2D6 metabolizer status. But the search really focused on children who had received codeine for a therapeutic purpose and had a death or an overdose. And so that excluded intentional overdoses, but we were left with six other cases that were identified in AERS that met the criteria but didn't include a metabolizer status. So there's really no way to know if these children were ultra-rapid metabolizers, but just to highlight a couple things here, three of the six children were treated for pain post-adenotonsillectomy, and all six of the patients died. But there is a limit to what we could -- oh, I'm sorry, one other thing. The time to event was one to two days,

which was consistent with what we saw in the other codeine patients.

We also did the AERS review of other opioids, and the review of the AERS database did not recover any robust cases of unexplainable or unconfounded death or opioid toxicity following use of Oxycodone, Hydrocodone, or Morphine in pediatric patients. So that review did not identify relevant cases.

So, at this point, we had a lot of -- we had the bulk of the cases that had been identified were post-adenotonsillectomy. But children are treated with codeine in other settings, potentially post dental procedures for orthopedic injuries and whatnot, and so we tried to understand or determine identify other sources of cases. And around the time that we released our drug safety communication in August of last year, shortly thereafter we heard from some folks at the American Academy of Otolaryngology and Head and Neck Surgery. And they actually had conducted a survey of their academy members looking for cases of bad outcomes following tonsillectomy, such as death or permanent disability.

This survey, the results are in press but I have some summary data. So there were eight pediatric cases that were classified as being related to narcotic medications. Seven of those cases the indication was obstructive sleep apnea, and one of them was chronic tonsillitis. There were underlying

conditions of Down syndrome in three patients and neurologic disorder in one. The outcomes were seven deaths and one anoxic brain injury. And the ultra-rapid metabolizer status there was one that was confirmed in a postmortem testing and one that was suspected due to high morphine levels. And the reference is here at the bottom of the slide.

I want to talk a little bit about drug utilization of opioids in the pediatric population, because this was another consideration that we wanted to look into as we thought about how we might address the risk of codeine in ultra-rapid metabolizers following adenotonsillectomy, because at this point that was really the primary setting in which we have observed these catastrophic cases.

So, in this first slide, what you can see here is in a pediatric population broken out by ages 0 to 1, 2 to 5, 6 to 10, and 11 to 17. You can see that codeine and Acetaminophen combination is the primary formulation of codeine that's being used. Codeine as a single ingredient was so infrequent as to not be visible on the slide. But in comparison to codeine Acetaminophen combination products, Hydrocodone Acetaminophen combination products are used much more in the older age groups and similarly in the younger age groups. Oxycodone Acetaminophen combination is fairly uncommon except in the older age group.

This next slide talks about what -- which specialties were prescribing the codeine and Acetaminophen combination. I actually took the single ingredient codeine off of the slide because there is very little to none. In -- primarily general practice/family medicine/doctor of osteopathy, that was the top prescribing specialty. That's the way that the drug utilization data combines those physicians together, so that's how they're grouped. For the codeine Acetaminophen -- oh, I didn't take the single ingredient off. Well, in any case, they were the most common prescribers.

The otolaryngologist was the top specialty for the codeine Acetaminophen in the oral liquid formulation, and I have the pediatricians, what the various -- how much percentage of prescribing that they accounted for. So it was relatively low; although, for the oral liquid formulation slightly higher.

On this slide it's very busy, but let me just point you to the otolaryngology -- there's a typo there but it's supposed to otolaryngology line. And again, for the liquid -- oral liquid formulations for the various combination products, you can see that the otolaryngologists account for substantial proportion of prescribing of the codeine Acetaminophen combination, Hydrocodone Acetaminophen combination, and the Oxycodone Acetaminophen combination. The pediatrics specialty, somewhat less so.

Moving on, this talks about the diagnosis data. And I'll just say that diagnosis data is derived from survey data of physicians who are -- participate in kind of a periodic effort to document what indications they're prescribing various medications for. So surgery follow-up was the most common diagnosis code that was associated with combination codeine Acetaminophen in all age groups. And then indications of acute tonsillitis and chronic tonsillitis and adenoids was also mentioned for the younger -- for all of the pediatric age groups, although at a relatively low frequency.

This slide has similar data for the other opioids that we looked at. So, for Hydrocodone and Acetaminophen combination, the tonsils with adenoids hypertrophy and acute tonsillitis was the diagnosis for 5 percent of the drug use mentions in the youngest age group, and then increased in frequency into the age 2 to 5 range, and decreased slightly in the 6 to 10 age group.

For Oxycodone Acetaminophen, it was associated with a small amount of drug use mentions in the oldest patient group but not in the younger patient groups. And for morphine there were no diagnoses -- diagnosis codes that -- for conditions related to tonsillectomy among the pediatric patients.

So, after considering all of the information that we were able to glean from the medical literature, from the Adverse

Event Reporting System reviews, and from considering other sources of information that we were able to get, and the drug utilization data, we made some regulatory actions that we took last month and described in a drug safety communication that was posted on February 19th. Those label changes include all codeine-containing products. So, although there is some codeine-containing products that are approved primarily for tension headache and whatnot and some for cough and cold, these changes are across all codeine-containing products. So there is a boxed warning that has the title "death related to ultra-rapid metabolism of codeine to morphine," and it has the text here on the slide. We also added a contraindication for post-operative pain management in children who've undergone tonsillectomy and /or adenoidectomy. And there are also modifications to warnings pediatric use and patient counseling information sections.

Now, the question came up earlier as to whether, you know, we could do genotyping, and, "Wouldn't that help us?" And I think we have not chosen to recommend routine genotyping for a number of reasons, and that are described on this slide.

So the first, and that we've already seen, is that extensive metabolizers can overlap with ultra-rapid metabolizers in the levels of morphine that they generate. And so if one was to genotype a child and they turn out to be an EM, there might be a over-confidence that the child would be safe with codeine

when, in fact, they may be able to generate high levels of morphine. So that, to us, was a very important reason to not recommend genotyping. But beyond that, the positive predictive value of the test is likely low, so many -- the numbers needed to screen in order to prevent one event as very high. And then a very practical reason: there is pre-operative -- and you probably know this better than I -- pre-operative lab tests are not generally done prior to adenotonsillectomy, and so it would be problematic to add a new blood test in that setting. So we've not gone with any kind of recommendation for genotyping.

And this really relates, in part, to where the contraindication comes from, because there's really no way to know who might get into trouble with codeine. And of course, we've also heard that 10 percent of children won't get any benefit because they're poor metabolizers. And so -- and we know that other -- there are alternate pain management treatments, and so that led us to take the actions that we've taken.

I just want to comment that, in an effort to communicate these changes, particularly for a drug that's been around a long time and is still fairly widely used, we -- as I mentioned, we posted an FDA drug safety communication. We have an FDA consumer update. We did a stakeholder outreach call with professional associations to alert them to these changes, and

then we distributed the information through channels that we have at FDA for communicating information, like the MedWatch, LISTSERV, Twitter, and Facebook.

And I'll stop there.

CHAIRMAN TOWBIN: Thank you Dr. Racoosin. Dr. Wagener.

DR. WAGENER: That was really excellent. Thank you.

So how do you get a drug off the market? I mean, it strikes me that codeine has -- you can -- all of this you showed us could be -- hydroxocodone could be used instead of codeine. It has its own risk factors too, but it seems like codeine is such an ancient drug that we're now identifying significant people that don't get adequate levels, significant people that may get toxic levels. It seems like it ought to come off the market.

DR. RACOOSIN: Yeah, I'm not really going to engage any further on that particular --

[laughter]

-- point of discussion at this point.

CHAIRMAN TOWBIN: I think Walt has a statement to make at this juncture.

DR. WAGENER: My question was strictly, "How is that done?" I mean --

CHAIRMAN TOWBIN: Yeah.

DR. WAGENER: -- is it possible for things like that?

CHAIRMAN TOWBIN: Well, hold on one second, because I think Walter's going to say something and that may be useful for the discussion.

DR. ELLENBERG: Yeah, just to bear in mind, when I said that this was just a presentation to the committee, there's a reason, is because we did not screen members of the committee for conflicts of interest, and so we need to be careful as to what is said --

DR. WAGENER: Again, it's a generic question. How do you get a drug off --

DR. RACOOSIN: So, in essence, any drug that would be considered would have a extensive assessment of the benefits and the risks of the drug, and that would be done prior to any kind of action in that regard.

CHAIRMAN TOWBIN: Dr. Rosenthal.

DR. ROSENTHAL: So just a quick question. You know, as -- well, maybe a few quick questions related to the label changes. So I appreciate that the label's been changed to represent the risk for people who are rapid metabolizers. Did the -- was the label also changed to represent the, I guess, new information about people who respond poorly, who do not derive an analgesic effect? That's my first question.

And my next question's a very -- is sort of a more generic labeling question, and that is, for a generic drug or for, you know, for a drug that has been around for all time, for a drug that, actually, in Canada, you know, it comes -- many of these formulations you can just get over the counter. They're behind the counter, but you can ask for them, but you don't need a prescription of any kind. Is it easier to make label changes for drugs that fall into that category than for drugs where there continues to be a patent or something like that?

DR. RACOOSIN: So let me address the first question. This particular labeling action was focused on the risk associated with ultra-rapid metabolism of codeine. So we have not instituted particular labeling changes related to poor metabolizers.

The second question is that there are -- so we've requested these labeling changes on, you know, that -- so the FDA Amendments Act of 2007 gave additional safety authorities to FDA, including the ability to require safety labeling changes. So this -- these labeling changes have been requested within that authority, and they're in the process -- so we request them and then, you know, they get processed. So we'll be working on that over the next few months.

But drugs that are the generic version of branded drugs, their labeling has to follow the branded drug, so they

have to have those changes made at the same time. For drugs for which there's no longer a branded version, they're still what's referred to as a "reference listed drug." So one of the generics, usually the one that was approved first, not always, is identified as the reference listed drug, and so they also have to make all of the changes. And so on the day that this labeling change went out, it went out to all of the branded drugs and then all of the reference listed drugs that are generics. The generic formulations that do have a branded product, the law says that that has to follow. So we'll do the branded first, and then the generic follows.

DR. ROSENTHAL: And -- I'm sorry -- and from a regulatory perspective, is it generally easier to make labeling changes to generic drugs than it is to drugs that are still -- that are not yet generic?

DR. RACOOSIN: No. I mean, the authority allows us to make the safety labeling changes across the --

DR. ROSENTHAL: The only reason I'm asking is because, you know, it has come up frequently where, you know, the agency is -- I think the expression is that the label belongs to the sponsor, and that we negotiate with the sponsor around the labeling changes. So, you know, I guess my question boils down to, are we really negotiating? Once drugs have become generic,

is there still this negotiation process, or is it just easier to make the changes?

DR. RACOOSIN: So since the FDA Amendments Act of 2007 and the safety labeling change authority, we don't have to use the word "negotiate" anymore. We require a safety labeling change, and the sponsor, whether it's a branded product or a generic product, they come back either with the changes requested or with a rebuttal. But ultimately, we -- FDA has the capability of ordering a labeling change. I'm not sure how often that's occurred. But that concept of having to negotiate is somewhat antiquated, because we're now in the era of the most recent safety authorities.

CHAIRMAN TOWBIN: Dr. Franco.

DR. FRANCO: Yeah. As a surgeon who has been in a group practice doing, what -- our group probably does 2,500 surgeries a year -- using codeine as our primary medication. You're a pediatric urologist. I would sort of not jump to the conclusion necessarily without having more data. And when we look at how our patients get managed for pain management -- and there may be some other issues that are here in play. You know, the tonsillectomy kids, when they come out they're in extreme pain. They may be getting a whole host of other medications that are maybe playing a role in this metabolism effect. While our pediatric urologic patients get Codal, okay, and their use

of codeine is primarily four to six hours later, once they've gone home and the Codal has lost its effect.

So I think we can't just necessarily jump and say that this is a horrendous drug and has to come off the market. We know it's specifically targeted to one particular group, and there may be other effects that are in play here.

DR. RACOOSIN: So let me just say, I didn't -- I was not -- I just want to be clear that I'm not the one that suggested that -- I came to talk about the changes that we've made in the post-adenotonsillectomy period, and I really, you know, want to be careful about where this conversation is going, because --

MALE SPEAKER: Good.

DR. RACOOSIN: -- I'm not the one who initiated this further discussion --

DR. FRANCO: No, I'm just -- I'm just answering --

DR. ELLENBERG: I have to step in. We can't continue that line of questioning on that --

DR. FRANCO: Yeah. No, I'm just answer Dr. Wagener.

DR. NELSON: -- because that's -- That's going beyond. We're outside of the compliance with federal law if we haven't screened you for conflict of interest. So you guys can carry on your conversation out in the hallway privately.

All right. So -- we just can't do that.

CHAIRMAN TOWBIN: Dr. Wagener, would you like to raise a nice, generic comment?

DR. WAGENER: Actually, I was going to ask, what are -
- of the CYP2D, what concomitant medications stimulate that pathway? In other words, can some of this be because children are on a second medication that actually --

DR. NELSON: Can I just -- you know, we really can't even talk about other products. There's been no --

DR. WAGENER: No, I'm just -- I'm not talking about a product. I mean, I think you totally misunderstand me. Let me finish, please. Let me finish. I think you've totally misunderstood. I've asked a couple of simple questions. One is how FDA functions in one way. And this one, I just simply want to know, for my own personal knowledge, what are CYP2D stimulators? That's a pretty simple question.

DR. RACOOSIN: CYP2D6, in general, is not an inducible enzyme, so it can be inhibited, but it cannot be induced. So that's not a likely mechanism for some of the things that we see.

ADJOURNMENT

CHAIRMAN TOWBIN: All right. I think that we're coming to the end. And actually, I think that we should adjourn. I want to thank all of you for your assistance today, throwing me lifebelts when they clearly were needed and helping us get through what I think was a pretty formidable agenda with some nuanced discussion. So thank you very much for coming. I hope everyone has a nice evening.

DR. YAO: Just one thing before you guys go. Sorry. On behalf of Diane in the Office of Pediatric Therapeutics, we do want to thank the committee, who's here, and for all of your work today. And just one plug: if you're able to stay for tomorrow, there is another neonatal subcommittee meeting to talk about neonatal drug development happening right here, starting at...

DR. NELSON: I think 8:00 a.m.

DR. YAO: 8:00 a.m., yeah.

DR. NELSON: For which there will be no product discussion, because we've not screened for any conflict of interest.

(Whereupon, at 5:17 p.m., the meeting was adjourned.)

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