

MEETING OF THE PEDIATRIC ADVISORY COMMITTEE
TO THE FOOD AND DRUG ADMINISTRATION

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Monday, May 16, 2011
Hilton - Silver Spring
8727 Colesville Road
Silver Spring, Maryland

The meeting was convened at 8:05 a.m., GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding.

MEMBERS PRESENT:

GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding

BRAHM GOLDSTEIN, M.D.

KATHLEEN MOTIL, M.D., Ph.D.

DANIEL NOTTERMAN, M.D.

ALEX RAKOWSKY, M.D.

MICHAEL D. REED, Pharm.D., FCCP, FCP

VICTOR SANTANA, M.D.

KENNETH TOWBIN, M.D.

CONSULTANTS/TEMPORARY MEMBERS PRESENT:

GARNET L. ANDERSON, Ph.D.

JATINDER BHATIA, M.D.

MARILYN EICHNER

KATHLEEN NEVILLE, M.D., M.S.

NORMA MARTINEZ ROGERS, Ph.D., R.N., FAAN

ALAN D. ROGOL, M.D., Ph.D.

JOSE RAFAEL ROMERO, M.D.

TOR A. SHWAYDER, M.D.

JEFFREY WAGENER, M.D.

ALSO PRESENT: WALTER ELLENBERG, Ph.D.,
Executive Director and Designated Federal Official

P R O C E E D I N G S

WELCOME AND INTRODUCTORY REMARKS

CHAIRMAN ROSENTHAL: Good morning, everyone. Thank you for joining us today for the Pediatric Advisory Committee meeting for the FDA. I apologize for a little bit of a late start. We've had some last minute changes, which we'll go through with everyone to be sure that, to the extent that we can be, we'll be a well-oiled machine moving through today's agenda. We have a number of important issues to discuss.

So why don't we start with introductions, and as we're doing this I'll just say that two of the Pediatric Advisory Committee members, Doctors Notterman and Santana, are not with us this morning and will be joining us at some point during the day today. So when they arrive we will introduce them as well.

So I'll start by introducing myself and then, so that I don't forget, we'd like to have the people who are on the conference call introduce themselves, and then we'll go around the room. So my name is Geof Rosenthal. I'm a pediatric cardiologist, professor of pediatrics, at the University of Maryland, and I'm chairing the Pediatric Advisory Committee meeting today.

Diane, I don't have my glasses on, but will you get us started.

DR. MURPHY: I'm Diane Murphy and I'm a pediatric infectious disease specialist. I'm the Director, Office of

Pediatric Therapeutics at the FDA.

DR. McMAHON: Ann McMahon. I'm a pediatrician. I'm the Deputy Director of the Division of Pharmacovigilance I in the Office of Surveillance and Epidemiology in CEDR at the FDA.

DR. COPE: Hi. I'm Judy Cope, pediatrician, epidemiologist, and I head up the safety team in the Office of Pediatric Therapeutics.

DR. GOLDSTEIN: I'm Brahm Goldstein. I'm a pediatric critical care physician, and I'm the industry representative to the committee.

DR. ROGOL: I'm Al Rogol. I am a professor of pedes at both the University of Virginia and Indiana University, and it is an interesting commute. And I am a pediatric endocrinologist.

DR. WAGENER: Jeff Wagener, pediatric pulmonary professor at University of Colorado.

DR. MOTIL: My name is Kathleen Motil. I'm from Baylor College of Medicine in Houston. I'm a pediatric gastroenterologist and double-degreed in nutritional biochemistry and metabolism.

DR. MARTINEZ ROGERS: I'm Norma Martinez Rogers and I'm a nurse and a professor at University of Texas Health Science Center in San Antonio.

DR. RAKOWSKY: Good morning. My name is Alex Rakowsky. I'm the IRB Chair in Nationwide Children's Hospital in Columbus, Ohio.

DR. ELLENBERG: Good morning. I'm Walt Ellenberg. I'm the Designated Federal Official for the Pediatric Advisory Committee, and with the Office of Pediatric Therapeutics.

CHAIRMAN ROSENTHAL: Can we hear the introductions of the folks who are on the conference call, please.

DR. CRAIG: Hi. I'm Eileen Craig. I'm a medical reviewer in DNEP.

DR. ROBERTS: Hi. My name is Mary Roberts. I'm also a medical reviewer in the Division of Metabolism and Endocrine, covering Crestor.

CHAIRMAN ROSENTHAL: Thank you.

Then, continuing.

DR. ANDERSON: Hi. I'm Garnet Anderson. I'm a biostatistician at Fred Hutchinson Cancer Research Center in Seattle.

MS. EICHNER: My name is Marilyn Eichner. I'm a nurse and also a patient and family representative.

DR. REED: Good morning. My name is Michael Reed. I'm a pediatric clinical pharmacologist and toxicologist. I direct that division at Akron Children's Hospital.

DR. NEVILLE: Good morning. Kathleen Neville. I'm a pediatric hematologist-oncologist and pediatric clinical pharmacologist at Children's Mercy Hospital in Kansas City.

DR. SHWAYDER: Tor Shwayder, pediatric dermatology at Henry Ford Hospital in beautiful downtown Detroit.

DR. BHATIA: Jatinder Bhatia, professor of pediatrics at Georgia Health Sciences University, formerly the Medical College of Georgia.

DR. ROMERO: Jose Romero. I'm a pediatric infectious diseases subspecialist at the University of Arkansas Medical Sciences, Arkansas Children's Hospital. I'm currently also the chair of the Vaccines-Related Biological Products for the FDA.

DR. ELLENBERG: At this time I will go ahead and read the opening statement for the meeting. I'd like to say good morning to everybody, to the members of the Pediatric Advisory Committee, members of the public, FDA staff. Welcome to the meeting.

The following announcement addresses the issue of conflicts of interest with regard 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 reported by the committee participants, it's been determined that those individuals who will be participating in each topic do not have a conflict of interest for the following products: Bepreve, Besivance, Cetraxal, Patanase Spray, Astepro Spray, Crestor, Welchol, Hiberix, Valcyte, and the topical calcineurin inhibitors Elidel and Protopic.

In addition, today the committee will receive a summary

of the recently-convened Pediatric Ethics Subcommittee meeting, which was held on May 11th. The Pediatric Ethics Subcommittee will provide -- the meeting was held to provide advice and to make recommendations on a hypothetical protocol involving the administration of sub-therapeutic doses of drugs or biologics to a healthy population of children. This was a non-voting meeting and there was no discussion of safety or efficacy for any specific drug and no company was under discussion at that meeting.

The ethical considerations addressed the following topics: assessment of risk of administering sub-therapeutic doses of a drug or biological product; the appropriate subject population to utilize for these studies on children; and the referral process for such protocols for review by a federal panel under 21 CFR 50.54.

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.

We note that Dr. Norma Martinez Rogers is participating as the consumer representative; Ms. Marilyn Eichner is participating as the patient-family representative. Doctors Bhatia, Shwayder, Romero, Rogol, Neville, and Anderson are participating as temporary voting members.

We would like to note the following: Dr. Notterman will be recused from the discussion of Protopic; Dr. Anderson will be

recused from the discussion of Lexapro; Dr. Romero will be excused from the discussion of Valcyte; Dr. Shwayder will be considered a voting member for all products, with the exception of the discussion on the issues of Protopic, for which he will be allowed to participate in the discussion, but as a non-voting member.

Dr. Brahm Goldstein is participating as a non-voting industry representative, acting on behalf of regulated industry. Dr. Henry Farrar, who will be here later on this morning, is participating as a non-voting industry representative on behalf of the pediatric health organizations.

With respect to all other participants, we ask 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 an open public session, which is scheduled to be at 1:30 this afternoon.

I'd like to remind everybody, if you would right now: for those around the table, please make sure that when you speak you turn on your microphones and then when you finish turn them off, so we avoid any kind of feedback over the speaker systems.

For those of you in the audience and those around the table, make certain that you either turn off your cell phones or at least put them on a muted status so they don't interrupt the meeting.

With that, I thank you and I look forward to a good

meeting. We'll continue with Jeff.

CHAIRMAN ROSENTHAL: Thank you. Thank you, Walt.

Just before we get started, I just want to point out once again that there are three binders of briefing materials -- the cumulative width is in excess of a foot -- for today's meeting. This is a great symbol for me of all that goes into preparing these meetings. I'd like to thank the agency for all of everyone's work.

The Office of Pediatric Therapeutics is, like many other areas of the government now, asked to provide support for the people of the United States with limited resources, and I think the Office of Pediatric Therapeutics has done a great job once again. So I want to just take a moment to acknowledge the fantastic work of everyone involved.

Just to briefly review the agenda for today, there will be some changes. We'll try and keep everyone on track. But we'll start, as scheduled, with the abbreviated presentations, and then we'll move along through the schedule. The presentation by Dr. Skip Nelson reviewing the Subcommittee, the Pediatric Ethics Subcommittee, will be moved to 11:15, so that presentation will go from 11:15 until probably around 11:45.

Then Novartis will share with us its presentation on Elidel. So the other presentations pertaining to the topical calcineurin inhibitors will be moved in sequence to accommodate the travel disruptions of a number of people who are going to be

participating in the discussions today.

So we apologize for these changes in the schedule, but the changes are necessary in order to assure that we have the most robust discussion of these topics.

One other point I'd like to make is that the agency for this meeting provided people around the table with information that was not redacted for some of the products. The agency did this at the request of the Pediatric Advisory Committee because many of the discussions of the committee in prior meetings have been encumbered by the lack of information due to redaction.

The information that was redacted is confidential, and so two comments about that. One is, please be careful if you're referencing materials that were non-redacted. The unredacted -- the information that was not redacted that would otherwise have been redacted is confidential information and should not be disclosed in this setting.

The other is that, because there's information that's considered confidential, for those of us that have received CDs with unredacted information on them, we are to turn that information back in to Walt at some time during the meeting or at the end of the meeting.

So thank you for that. I will say that reviewing the information that was unredacted for me was quite helpful in several instances, and so I'm appreciative that we're trying this. But I would just ask the committee to please be extra careful

that we don't violate any confidences during the meeting.

One other point. We will have a few breaks during the day and we'll have lunch, and it's important that we not discuss the matters of the meeting in those contexts. The agency requires and for this process to work there is a requirement for an open and transparent discussion. Really, all of the information that - - anything that would be said outside is better said into the microphone so that the agency and others can benefit from people's insights and reflections.

So please share your ideas inside the forum and please abstain from having discussions outside the forum.

Dr. Towbin, will you -- Dr. Towbin has arrived. He's made his way around the Beltway, so thank you, Ken.

DR. TOWBIN: I apologize for my delay. I'm Kenneth Towbin. I'm a child and adolescent psychiatrist in the intramural program with the National Institute of Mental Health.

CHAIRMAN ROSENTHAL: All right. Dr. Murphy, would you like to speak for a moment? Let me just take a moment to introduce Dr. Murphy for those of you who don't know her. But Dianne Murphy is the Director of the Office of Pediatric Therapeutics at the FDA, and she's been with the FDA since 1998. She's also served as the Director of the Office of Counter-Terrorism and Pediatric Drug Development, the Associate Director for Pediatrics, and Director of the Office of Drug Evaluation, with oversight for all of the divisions involved with anti-

microbial therapeutics.

Dr. Murphy received her medical education from the Medical College of Virginia and she completed her pediatric residency at the University of Virginia, with a fellowship in infectious diseases at the University of Colorado. She's been very productive academically, making many contributions, and is the editor of a book on office laboratory procedures.

Dr. Murphy.

PEDIATRIC ADVISORY COMMITTEE RETIREMENTS

AND OTHER FDA UPDATES,

BY DIANNE MURPHY, M.D.

DR. MURPHY: I want to thank everybody who made it around the Beltway. We all had those challenges this morning. As has been noted, we apologize for having to change the schedule, but we can't control the weather and a number of flights have been affected. So we are trying -- and we appreciate Novartis's cooperation with us in changing the order of the presentations.

We were going to give out some plaques, but since people can't get here we're just going to not do that this morning.

I've noted this morning, listening to the names as we go around, that we have a number of people who've not been on this committee before, and we have some processes that are different for safety reviews than it is for a product review. So if you have questions, you don't really understand what's being asked of you, please feel uninhibited to ask. We'd much rather have you ask the

question and be able to make your comment and vote the way, as informed as possible.

Judith is going to, Cope, is going to go ahead and explain a little bit more about the abbreviated, I think, or make sure the committee understands what we mean by "abbreviated," when you got two binders of material on a large number of products that we have designated for "abbreviated."

So I will turn it over to Dr. Cope now. Thank you.

CHAIRMAN ROSENTHAL: As Dr. Cope's coming up to the microphone, I'll just introduce her as well. Dr. Judith 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. Then after several years in academic medicine and in clinical practice, she received an MPH in epidemiology and biostatistics.

Dr. Cope.

ABBREVIATED PRESENTATIONS,

BY JUDITH COPE, M.D., M.P.H.

DR. COPE: Thank you. Good morning. Thanks to all of you for being here today. If you look at your agenda, you will note that there are eight products that we're going to start off with that are abbreviated. So I know many of you have been

through this before, but, as Dr. Murphy highlighted, we know some of you are new, and it's been a few months since the last safety reporting advisory committee meeting.

So I just want to highlight that all of these eight products we have put in a group called "Abbreviated," but they have all undergone the pediatric-focused safety review as mandated by Congress. As was mentioned earlier, you got two full binders of all these products. You got all the materials on the labeling, the earlier clinical trials, and, importantly, the updated safety and use reviews.

What we like to do is when we go through, when the safety team meets through our meetings and go over the reviews and what we think the issues are at hand, we have pulled aside an abbreviated category for drug products where sometimes the product is not really marketed at all, there might be little use in the product population, when we go through the review, the AERS reports that FDA has received about adverse events there are very few, if any, there were no deaths, the literature's been searched, there's no safety signals that emerge when we review, when we discuss.

When those instances happen and we see that the safety labeling or the labeling for the product seems fine, we then created this category, so that we in our own review that FDA sees that there are no emerging safety issues and that we see that for this product at hand that the standard ongoing safety monitoring

should be continued, but there are no emerging issues, and we would ask you to vote whether you would agree with this.

So that's why I have listed these eight products that we felt fell into that category. As you heard, there were a couple people on the phone, some of our endocrinology experts, and our other FDA scientist technical experts are here in the audience regarding these products from the various divisions, pulmonary, ophthalmology, endocrine, and the Division of Reproductive and Neurologic Products.

So what I'd like to do then is have you vote one by one for each of these products. You have all the reviews. This is your opportunity to ask questions, if you should have any, of the FDA staff that are here. But I will turn it over to Jeff and we'll just take it one by one, where each product will be named and then does the committee concur with our FDA plan to continue ongoing safety monitoring.

DR. MURPHY: Judith, we need the FDA representatives who are here for the various products. I know Wiley is here for ophthalmology. Would Peter and Wiley come on up to the table.

DR. COPE: Steven Voss, Dr. Voss.

DR. MURPHY: Yes.

DR. COPE: And I think that some of the endocrinologists are here, and there are some others on the phone: Eileen Craig, Mary Roberts.

DR. MURPHY: Let me have them introduce themselves, if

that's okay.

CHAIRMAN ROSENTHAL: Yes, please.

DR. MURPHY: We want you to know we put a lot of effort into this, and these people are prepared if you have any questions.

DR. CHAMBERS: I'm Wiley Chambers. I'm the Deputy Director for the Division of Transplant and Ophthalmology Products.

DR. VOSS: I'm Steve Voss. I'm a medical reviewer in the Division of Reproductive, Urologic, covering Actonel.

DR. STARK: Good morning. I'm Peter Stark. I'm a medical reviewer in Pulmonary, Allergy, and Rheumatology Products.

CHAIRMAN ROSENTHAL: Thank you all.

All right. So we've all received and have had an opportunity to review the materials that have been distributed on these, for these eight different products. What I'd like to do is, first let's take them one at a time. So any questions, comments, concerns regarding Patanase Nasal Spray that we should discuss?

(No response.)

CHAIRMAN ROSENTHAL: All right. Then what we'll be voting on is whether these products should be returned to the routine monitoring protocols at the agency. So all in favor of returning this to -- I'm sorry. You were voting?

DR. ROGOL: I was voting too quickly.

CHAIRMAN ROSENTHAL: That's good, get us going here.

So all in favor of returning Patanase Nasal Spray to routine surveillance and safety monitoring?

DR. SHWAYDER: I have a question.

CHAIRMAN ROSENTHAL: Yes?

DR. SHWAYDER: I was desperately trying to find the thing, that one of nasal sprays there was a little uptick in nasal septum perforations. And I was desperately trying to go through it to see whether that was also present in the placebos. Can someone from the FDA refresh my memory, because it's all kind of a blur in my brain at the moment.

DR. VOSS: I think that's related to azelastine, the second product.

DR. SHWAYDER: Azelastine, fine.

CHAIRMAN ROSENTHAL: All right. All in favor of Patanase returning to routine monitoring, please raise your hand.

(A show of hands.)

CHAIRMAN ROSENTHAL: Anyone opposed?

(No response.)

CHAIRMAN ROSENTHAL: Let's go around the table with our votes. Can you get us started, please?

DR. ROGOL: Al Rogol. I vote yes. Is that what you're asking?

DR. WAGENER: Jeff Wagener, yes.

CHAIRMAN ROSENTHAL: Yes. I had my glasses off, so I couldn't see either your face or your name. But I saw your hand earlier.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Concur.

DR. ANDERSON: Garnet Anderson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: All right. Let's move right along to Astepro Nasal Spray. Were there questions regarding this product? Dr. Shwayder?

DR. SHWAYDER: I'm desperately trying to find the statistics in the CD you sent me regarding the nasal perforations. Can someone highlight that for me? Was it statistically significant and was it seen in the placebos?

DR. STARK: I'm not sure -- this is Dr. Peter Stark, Pulmonary, Allergy, Rheumatology. I see the results of the long-term safety trial. I'm not sure if that's what you're talking about, because in that trial there were no nasal septal

perforations. We looked very closely for nasal septal perforation in all of these intranasally administered products, but I'm not sure to what you're referring.

DR. SHWAYDER: I might just be misremembering it. Dr. Wagener?

CHAIRMAN ROSENTHAL: Yes, please, Dr. Wagener.

DR. WAGENER: So I actually had a similar question. I think the story here is that in a previous product they experienced nasal perforations. This is a reformulation that has removed one of the substances that was in the previous product, and they did not report nasal perforation with this product.,

I guess my question to the FDA is, if it returns to routine monitoring with the new product how frequently does that occur and, since it's now in a pediatric age range, are we going to risk with all of our data based on a single 12-month study. Some of these patients will be receiving this therapy maybe for much longer. So just technically, how is that handled?

DR. STARK: Can you just repeat that question, because I'm not sure I understand what you're asking.

DR. WAGENER: In the previous product there was some trouble with nasal perforation. In the current product, based on a one-year study, there was no nasal perforation seen. I believe the number of patients was just over a hundred. In children, who

may have a more sensitive nasal mucosa, is there a risk going to routine monitoring that we will miss a signal of nasal perforation occurring after children have been on this therapy for more than 12 months?

DR. STARK: We do look at 12-month safety studies for all of these products. So Astepro had a 12-month study. Patanase has an ongoing 12-month safety study that was a required study at approval.

DR. WAGENER: Right. This on the azalastine, not the Patanase. This is the Astepro Nasal Spray.

DR. STARK: We do continue ongoing monitoring, but we don't go beyond 12 months in terms of safety evaluations routinely.

DR. WAGENER: Right, I realize that. But the vote here is whether to put it on routine monitoring, as opposed to up to now I assume there's been a more vigilant monitoring process. Is there -- will we still be picking up any of these nasal perforation issues?

DR. McMAHON: This is Ann McMahon in the Office of Surveillance and Epidemiology, Division of Pharmacovigilance.

I'm thinking that maybe what you're referring to is the ongoing vigilance with respect to looking at AERS data. Is that what you're referring to?

DR. WAGENER: Correct. I just want to make sure we're not going to miss nasal perforation based on --

DR. McMAHON: Yes, absolutely. We were in our analysis of the AERS data over the last period of time, which was about a year, we were particularly looking for this. It was one of the adverse events that we were looking for. And that will continue to be the case.

We don't necessarily refer to it per se as a study, because it's not a controlled trial. We're looking for adverse events that are spontaneously reported.

CHAIRMAN ROSENTHAL: Thank you. So may I just clarify for a moment? So I think what I'm hearing is that if we return Astepro to routine surveillance then we will be looking for nasal perforation among the other safety signals that might come up through the routine monitoring process.

DR. STARK: This is Dr. Stark again. Yes, that is absolutely correct. We followed these products beyond this one-year safety reporting to you. On a regular basis, they're required for a certain period of time to submit quarterly reports, and then it goes to yearly reports. And we review them regularly.

DR. MURPHY: Since there are a number of new members, let me just -- because this is going to come up again and again. What the pediatric-focused safety review does is that Congress said, because we're getting all these products now that everybody's been using off label and we're going to get them now labeled, whether they were successful or not when we did pediatric studies, were there specific pediatric issues?

So that's why we refer you back to the label, because if something was found in those studies it would be in the label. So first thing to understand is, if it's in the label we already sort of know that there has been something that's come up.

The second thing, though, is that, as you noted, many of these studies are short-term and products are obviously used longer term. So the system is set up once a product is approved and out on the market or gets labeled for children that there's this ongoing monitoring that you're hearing about.

Normally in our training we go through what are the strengths and what are the weaknesses of this system. What we do with this focused review, though, that Congress has said we will do is, we make sure that we go in and we pull out all the pediatric adverse events, because we know the pediatric adverse events are a lot smaller part and you really have to go in and pull them out.

So when we do that, though, if you'll look, we have a table that we will give you, all the adverse events for children since the product was marketed. So we try to make sure we go back and we capture and list that number, anyhow, that we go back and capture that number.

If it looks like there are deaths, serious AEs, the things the committee has asked us to focus on, then that won't be normally abbreviated. So what you've pointed out here is that we have something that's not a death, may or may not end up getting

you hospitalized, so that is where you would end up in the serious. In that situation, we've looked at it and we saw it really wasn't any different than what we thought we saw, we expected may happen with some children. But obviously people would be concerned.

So it gets tagged, if you will, what Ann, Dr. McMahon, was saying, that this is something that the group knows might be an issue and would be looking for. So when you vote that it's going to go back to standard safety monitoring, that means that there's a group in the Center for Drugs Safety -- I'm sorry, Surveillance Group, that has these products. They know that this might be an issue and will continue to monitor them.

So if something happened that they thought, uh-oh, all of a sudden we're seeing a lot of kids having this problem, they would come to us. So the routine surveillance doesn't mean that nothing else is going to happen, and particularly if it's already been identified as an issue.

Does that help?

DR. WAGENER: Yes, that's very helpful. I guess the question would be, is there -- is it fairly sure that that surveillance occurs quite regularly? I mean, you follow a huge number of drugs and this would be one with a new preparation that's going to be used in children, I'm sure, where a signal may come up a year from now or two years from now. Is that well within the standard monitoring?

DR. McMAHON: We have individuals whose job it is to monitor a certain portfolio of drugs, and the reports for those drugs for that person go into what we call an in box. And they look at those reports daily, weekly. So knowing that this is an issue, this would be something that would be flagged.

CHAIRMAN ROSENTHAL: Dr. Stark.

DR. STARK: Thank you.

Beyond what you're just hearing about, the divisions also get those reports. We get the quarterly and yearly pediatric reports from the companies as well, and we look at them very closely. This is an event that my division, Pulmonary, Allergy, Rheumatology, looks at very closely for any intra-nasal product, both during the initial review as well as a post-marketing event, because it's an event of concern.

CHAIRMAN ROSENTHAL: So can I move us along here, unless there are other pressing comments?

DR. MURPHY: Just one last thing. You heard us try to say we think that this will be followed because it's already noted as something. If, however, the committee -- I have to say this. If the committee thinks, well, gee, we're still a little worried, we really want to know that you, particularly for children, have pulled this out and looked at it again in a couple of years or whatever, you can say that.

So I just wanted to make clear the committee has that

prerogative. What you'll hear from us is, when we're trying to tell you that one of the reasons "Abbreviated," we think we've identified it, we think it will be followed, but that's still your prerogative. So I wanted to make sure that that's clear.

CHAIRMAN ROSENTHAL: All right. Further discussion on whether this can move forward to a vote?

(No response.)

CHAIRMAN ROSENTHAL: All right. So let's vote, and the vote will be to see whether Astepro can return to routine safety surveillance as it's been described by our agency representatives today. All in favor?

(A show of hands.)

CHAIRMAN ROSENTHAL: Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: All right. Dr. Romero, will you get us started this time?

DR. ROMERO: Jose Romero. Approve.

DR. BHATIA: Jatinder Bhatia. Approve.

DR. SHWAYDER: Tor Shwayder. Approve.

DR. NEVILLE: Kathleen Neville. Approve.

DR. REED: Michael Reed. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. ANDERSON: Garnet Anderson. Approve.

DR. TOWBIN: Kenneth Towbin. Agree.

DR. RAKOWSKY: Alex Rakowsky. Agree.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Agree.

DR. MOTIL: Kathleen Motil. Agree.

DR. WAGENER: Jeff Wagener. Agree.

DR. ROGOL: Rogol. Agree.

CHAIRMAN ROSENTHAL: Okay, thank you.

Let's move along to the next agent, then, Bepreve. Some of these pronunciations, I have to decide how many syllables the words have.

So for Bepreve, any discussion or questions before we move ahead with a vote on whether this can be returned to routine safety monitoring?

(No response.)

CHAIRMAN ROSENTHAL: I'm not seeing any hands. All right, all in favor of moving Bepreve on for continued routine safety monitoring, please raise your hand.

(A show of hands.)

CHAIRMAN ROSENTHAL: Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: All right. Dr. Rogol, will you get us started.

DR. ROGOL: Rogol. Yes.

DR. WAGENER: Wagener. Approve.

DR. MOTIL: Kathleen Motil. Approve.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Agree.

DR. ANDERSON: Garnet Anderson. Approve.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: All right. Questions or discussions pertaining to Besivance?

(No response.)

CHAIRMAN ROSENTHAL: Don't be shy. This is our chance. So these abbreviated reviews are categorized in this way because the agency hasn't recognized a significant safety signal, as Dr. Murphy was just saying. But we don't want to stifle conversation or discussion if anybody has anything to bring up on these agents.

So no questions? All right, let's go ahead with the vote. All in favor of returning Besivance to routine safety monitoring, please raise your hands.

(A show of hands.)

CHAIRMAN ROSENTHAL: Thank you.

Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: All right, I'm not seeing any.

Let's go around the table. Dr. Romero?

DR. ROMERO: Jose Romero. Agree.

DR. BHATIA: Jatinder Bhatia. Agree.

DR. SHWAYDER: Tor Shwayder. Agree.

DR. NEVILLE: Kathleen Neville. Yes.

DR. REED: Michael Reed. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. ANDERSON: Garnet Anderson. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. ROGOL: Al Rogol. Yes.

CHAIRMAN ROSENTHAL: Thank you.

Next, next product is Cetraxal. Any questions, comments, concerns following our review of all the materials that we've received for this product?

(No response.)

CHAIRMAN ROSENTHAL: Seeing no hands, let's vote to see whether we believe that we should return this to routine safety monitoring. All in favor of returning this to routine safety monitoring?

(A show of hands.)

CHAIRMAN ROSENTHAL: Thank you.

Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: I'm seeing no hands. Dr. Rogol?

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener, yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. ANDERSON: Garnet Anderson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: Thank you very much.

Next product is Crestor. Discussion, questions? Yes,
Dr. Shwayder.

DR. SHWAYDER: Okay. Well, I have one of these questions, not about safety, but as a dermatologist. Does anyone know whether decreasing cholesterol really reduces the risk of stroke and arterial revascularization procedures? Do they have the 20-year study on that? Or are we, like in my division, putting on sun block and saying 50 years from now we'll find out

whether it reduces basal cell carcinomas?

You're all shaking your head like nobody knows whether reducing cholesterol does anything for other than the Framingham study in 55 year old fat men with diabetes. Okay. Fine, I think that answers my question.

DR. MURPHY: We have some people --

DR. SHWAYDER: We're all whistling past the graveyard.

DR. MURPHY: We have some people from Metabolic on the line, if they would like to say anything, because there's been a lot of controversy, looking into sub-populations, other types of studies ongoing. Not my area of expertise, but I would hope that people from Metabolic might be able to provide some additional information.

DR. ROBERTS: Hi. This is Mary Roberts. I'm covering for Crestor in the Division of Metabolism and Endocrinology.

Right. We have discussed this issue and we think it is a valid one, what the risk-benefit profile is for statins long-term in children. We know that in children the statin use reduces LDL. What that translates into long-term in terms of cardiovascular benefit, we don't have those studies.

However, when you look at how we would get at that answer, you would have to have a very large sample size, the length of the study would be decades. The at-risk population is really heterogeneous, so we don't know exactly what population would be the best to study, and the ethical and logistical issues

associated with having a placebo group long-term is controversial.

So we have looked at this and right now I think that that would be a study that would be difficult to do at this point.

CHAIRMAN ROSENTHAL: So it seems as though there are times when efficacy will be inferred in pediatrics in some way when the evidence in adults seems pretty solid. So this may sort of fall into that category as well.

DR. ROBERTS: Yes, and we do have studies in children from 10 to 17 years of age with heterozygous familial hypercholesterolemia, and at 20 milligrams of Crestor the LDL is reduced 50 percent. So we assume that that reduction will have the benefit that you see in the adult population.

CHAIRMAN ROSENTHAL: Okay, thank you.

Further discussion on Crestor?

(No response.)

CHAIRMAN ROSENTHAL: All right. Any discussion about any of the safety signal that was seen in the documents that were distributed to us?

(No response.)

CHAIRMAN ROSENTHAL: No. Would people be comfortable returning Crestor to the routine safety monitoring program? All in favor?

(A show of hands.)

CHAIRMAN ROSENTHAL: Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: I'm seeing no opposition. So I forget whose turn it is. Dr. Romero, will you get us started?

DR. ROMERO: Jose Romero. Agree.

DR. BHATIA: Jatinder Bhatia. Agree.

DR. SHWAYDER: Tor Shwayder. Agree.

DR. NEVILLE: Kathleen Neville. Agree.

DR. REED: Michael Reed. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. ANDERSON: Garnet Anderson. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. RAKOWSKY: Alex Rakowsky. Agree.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Agree.

DR. MOTIL: Kathleen Motil. Agree.

DR. WAGENER: Jeff Wagener. Yes.

DR. ROGOL: Al Rogol. Yes.

CHAIRMAN ROSENTHAL: Thank you.

Let's move on to Welchol. Any discussion of the safety information that was distributed? Yes, Dr. Wagener?

DR. WAGENER: So my understanding is this is a medication that is well shown in adults to decrease cholesterol. They've now prepared a granular form, as opposed to a tablet form, so it can be used in a younger age group. I guess my concern is that one of the things that's known to be a potential side effect is reduction of Vitamin E and other fat-soluble vitamins, which may be of particular importance to brain development in children

under age 3.

Since it's available as a powdered form or a granular form, is there some way to separate out those potential risks for children under age 3? And are we monitoring for that?

DR. CRAIG: This is Eileen Craig and I'm from the Division of Metabolism and Endocrinology. Certainly we look at all of the adverse events reports that come in. Welchol is not -- this would be off-label use because it's labeled for children 10 and older. But certainly we get all the adverse events that come in and, as has been mentioned previously, it is monitored, and we do see, when it's available, the ages of the children. So we would be looking at this data.

DR. MURPHY: If you felt that the agency should pull out the under 10 and look at off-label use in a couple of years, you can ask for that. Again, there are new members, so I'm just trying to make sure everyone understands their options. But as was pointed out, that's not what has been studied and that's not what it's labeled for. But as we know, in pediatrics that doesn't stop us from using drugs if we think we need to use them.

So if there's a concern -- we had one time the committee wanted to come and look at just that, a certain population under the labeled age and see what was going on. That is an option. So again, I'm just explaining your options.

CHAIRMAN ROSENTHAL: Dr. Wagener, would you like to?

DR. WAGENER: I think this is one where I actually would

have some concern. It's not a distrust of industry, but the fact that it's a granular preparation now -- 10 and above, you could have handled with just a tablet. As a powder or granule, it opens it up so easily for off-label use that I would think if in 2 years at least we know information on the amount it's being used in the younger child, because very honestly I don't know how you can assess Vitamin E deficiency-related neurocognitive development problems based on an adverse event reporting system.

But I think it would be advisable for the committee to hear within the next 2 years what utilization is occurring under age 10.

CHAIRMAN ROSENTHAL: With a plan -- just to follow up then, with a plan to try to help the agency decide whether to work with the manufacturer to develop more detailed studies that would look for some of these neurocognitive effects.

DR. WAGENER: It could either be that or the potential of labeling to give a warning of some type that says if it's going to be used in younger children at least monitor vitamin levels, something of that, which was done during these studies, I might say.

CHAIRMAN ROSENTHAL: Do others around the table feel that that would be reasonable as well? Any other comments? Yes?

DR. BHATIA: In principle I agree. However, the Vitamin E deficiency is a rare event and we are now talking about off-label use. In neonatology, everything we use except for two drugs

are off-label. So it depends how the committee wants to look at it, if the charge is to look at what is on label, versus the charge is to look at the entire spectrum. They are two different issues.

DR. REED: I think the label, if you look at the label, the label itself does comment on these deficiencies. My concern would be -- and I agree with my colleague as to the reality of looking at neurocognitive effects when there's no control in this at all across some time frame. And we fully appreciate the socioeconomic impact on that, too.

So I think it's an important issue. I just don't know that it's anything realistic. And I do feel a little more comfortable at least seeing it boldly on the label, not specific to infants, but to vitamin deficiency.

CHAIRMAN ROSENTHAL: Dr. Wagener, are you comfortable with the way that the label describes this?

DR. WAGENER: Yes, I think it does do a reasonable job there. Again, I think the only question is that the main risk group would be the younger child. And knowing whether this new preparation or this new available preparation would be increasing use in younger children would be the important point.

So numbers of people receiving the drug is really the most important monitoring. If a significant increase occurs in the young child, then it's our onus to think of safety in that age group.

CHAIRMAN ROSENTHAL: Would people like to -- would others like to see the utilization in kids younger than 10, in say a year or two? Would that be a difficult thing for you to provide the committee?

DR. MURPHY: It's never difficult for our group.

(Laughter.)

DR. MURPHY: It's just the priorities. I think that I would not suggest one year. I would give it longer, that we could look at the use in the under -- but I can tell you, if we're going to come back to you with the use, it would be very hard for us not to look at the adverse events, too. So that's really what you're asking for, and that's fine. But that's what I would frame it, is that you're really looking at the use. And we could to see if there's anything else.

But as you said, this is adverse events reporting for neurocognitive, and if you have issues it's going to be very, very difficult to ascribe anything to them. If you want us to just bring you the use back, we could do that and then we could discuss whether we should do a study or do further assessments. We could do that, too.

CHAIRMAN ROSENTHAL: So maybe a reasonable approach would be for the agency to look at utilization and if the utilization is extremely low then the adverse event question is less relevant.

Yes, Dr. McMahon?

DR. McMAHON: Ann McMahon. Just to -- I know you're all aware of this, but just to underline the fact that we do have current use data in that age group, yes. So you're talking about following that up.

DR. WAGENER: Right. Just realize that we have current use data, but this preparation is fairly new and it's one that would be easy to use in younger children.

CHAIRMAN ROSENTHAL: Dr. Motil?

DR. MOTIL: It seems to me that Vitamin E is a relatively simple measurement to make, and so in the surveillance it would be prudent, obviously, to look and see if people who are using this drug in the very young population are concomitantly measuring the vitamin E, given the warnings, before jumping to conclusions about neurocognitive behavior.

CHAIRMAN ROSENTHAL: Dr. Shwayder?

DR. SHWAYDER: Isn't it all fat-soluble vitamins you're worried about?

DR. MOTIL: Vitamin E is -- in the fat-soluble world, Vitamin E is usually the major problem, along with Vitamin D. Vitamin A is almost never an issue for us.

So it's very simply measured. It's sort of the poor man's way of looking at malabsorption.

DR. SHWAYDER: I might also add that every time there's a new hammer everything looks like a nail. It happens in dermatology all the time. So I'm sure if you have a

biosequestering agent you'll start using it, I don't know, for hyperbilirubinemia or something. You could see it in the neonate pretty soon. So it's probably not a bad idea to continue monitoring it.

DR. McMAHON: So I'm not sure if there's anyone here from the drug utilization group in the OSE. I guess not. But so I would want to ask those folks exactly what they can and can't do in terms of looking at concomitant use with those agents. But it seems like certainly a reasonable request.

CHAIRMAN ROSENTHAL: All right. Well, other discussion? Yes, Dr. Rakowsky?

DR. RAKOWSKY: How much granularity can we get as far as ages? Because if we're looking at just less than ten, that's -- you're more interested, I guess, in like less than two or less than four. Is there a way to pull that out also, or are we just going to get a bulk number? If it's all nine and ten year olds getting this, then I don't think the concern is there as much.

DR. McMAHON: Yes, because when the drug utilization group does the reviews for this committee we routinely talk about which age brackets we can zero in on, and we often look at zero to one, one to two, whatever the appropriate brackets might be.

There are limitations regarding the age brackets, and again I would rather defer to the utilization people about exactly which limitations they have for age brackets. But they do look at less than one as an age bracket, yes.

CHAIRMAN ROSENTHAL: Yes?

DR. NEVILLE: Just a question to help me understand this better in terms of age. When would this be considered for use, even off-label, in patients less than one or one to three? I mean, I understand familial hyperlipidemia, but does anyone -- would anyone use this within the scope of practice?

CHAIRMAN ROSENTHAL: I'm not -- well, GI and cardiology perhaps, but we don't really -- yes, Dr. Motil?

DR. MOTIL: Realistically, I don't think any one of us use the statins in the low age group. We don't even begin to think about it until the pre-adolescent. It's usually dietary, dietary, dietary, and dietary.

DR. NEVILLE: I guess then my question is how worth is it to look at this utilization and potential adverse events if people -- if this is not really used within the scope of practice?

CHAIRMAN ROSENTHAL: I think the concern -- I think Dr. Wagener's concern is that with this new formulation the utilization may increase. Is that reasonable?

DR. WAGENER: You would expect this would be used in similar distribution to statin use, at least as far as cardiovascular use. Indeed, statins are now being used in younger children, not only with familial hypercholesterolemia, but with other causes. So I think it's a growing concern.

CHAIRMAN ROSENTHAL: So we've talked about -- yes, Dr. Murphy?

DR. MURPHY: Maybe you're getting ready to do this, Geof, but I just want to summarize what I think your question. Right now, the way I'm understanding is what the committee would like us to do, understanding all the limitations, is simply a use review. And then if we see anything in the use review, we will discuss at the next meeting what else might need to be done; and to definitely look at the younger, see if we can break out the younger age group and the reasons it's being used.

But other than that, it's only a use review that we would need to bring back.

CHAIRMAN ROSENTHAL: Yes. And I think also that the committee will defer to the agency around the time frame that would be reasonable for this, for that review. We don't want to - - we don't want to artificially create a time frame that's so short that you won't increase the understanding of utilization.

DR. MURPHY: We say that because it takes us at least a minimum of six months. So we've got to give ourselves enough time to get -- to see what the use would be.

CHAIRMAN ROSENTHAL: Okay. So for now are we comfortable returning Welchol to routine safety monitoring? I'm seeing heads nodding yes. Can we vote? All in favor?

(A show of hands.)

CHAIRMAN ROSENTHAL: Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: I don't see any opposition to this.

Let's go around the table. Dr. Rogol?

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener. Yes, recognizing the review will come back.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Yes, with the caveat of being interested in that use review.

DR. ANDERSON: Garnet Anderson. Yes, also supporting the use review.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: All right. And the last agent for the abbreviated reviews is Actonel. Discussion about any of the information that we received on Actonel?

(No response.)

CHAIRMAN ROSENTHAL: No. Would everyone be comfortable returning Actonel to routine safety monitoring? All in favor?

(A show of hands.)

CHAIRMAN ROSENTHAL: Any opposition?

(No response.)

CHAIRMAN ROSENTHAL: Dr. Romero?

DR. ROMERO: Jose Romero. Approve.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. REED: Michael Reed. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. ANDERSON: Garnet Anderson. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. ROGOL: Al Rogol. Yes.

CHAIRMAN ROSENTHAL: All right. Now we will be moving along to the Hiberix discussion, and Dr. Farizo will be presenting the first presentation, the review of pre-licensure safety data.

TELECONFERENCE VOICES: Eileen Craig is now exiting.

TELECONFERENCE VOICES: Mary Roberts is now exiting.

CHAIRMAN ROSENTHAL: Okay, and that's the end of our teleconference. So we can check that off the list.

Dr. Farizo is a medical officer in the Division of Vaccines and Related Product Applications at FDA's Center for Biologics Evaluation and Research, in the Office of Vaccines

Research and Review. Dr. Farizo attended medical school at Louisiana State University and she trained in pediatrics at Duke University Medical Center.

During her 18 years at the FDA, Dr. Farizo has reviewed a wide variety of vaccines, but she continues to focus primarily on pediatric combination vaccines. And we're happy to have you here today to present this talk.

HIBERIX [HAEMOPHILUS B CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE)] REVIEW OF PRE-LICENSURE SAFETY DATA

DR. FARIZO: Thank you. Good morning. My presentation will be a review of pre-licensure safety data on Hiberix, and it will be followed by a presentation on post-marketing safety surveillance after licensure.

(Screen.)

I would like to begin with a brief background on Hiberix specifically, as well as Hib conjugate vaccines in general. Prior to licensure of Hiberix in 2009, we had had substantial experience with Hib conjugate vaccines in the U.S. over two decades. A Hib conjugate vaccine was first licensed for use in U.S. children in 1987, approved for use in children beginning at 18 months of age.

Subsequently in 1990, the first Hib conjugate vaccine for use in infants was approved.

(Screen.)

Hiberix was approved at a time when we were experiencing a nationwide shortage of Hib conjugate vaccines in this country

due to manufacturing problems and suspended production of two licensed Hib vaccines.

(Screen.)

Because of the shortage, in December 2007 CDC recommended deferral of routine booster immunization against invasive Hib disease for all children who were not specifically at high risk.

By June 2009, there was an increase in the U.S. supply of two other licensed Hib vaccines, which allowed CDC to reinstate routine booster immunization. By that time, the supply was still not sufficient for mass catch-up and vaccination of children whose doses had been deferred.

In August 2009, Hiberix was approved for booster immunization and a month later CDC recommended recall and vaccination of all children whose booster dose had been deferred during the shortage.

(Screen.)

During the vaccine shortage, we initiated discussions with GlaxoSmithKline about the Hib conjugate vaccine, which, although licensed in many other countries, did not have a specific clinical development program in the U.S.

Hiberix contains capsular polysaccharide from haemophilus influenza type B and is conjugated to tetanus toxoid.

It contains no preservative or adjuvant. The formulation of Hiberix is similar to that of another U.S.-licensed Hib vaccine

that has been on the market since 1993.

(Screen.)

Hiberix was first licensed in Germany in 1996 and subsequently licensed in approximately 100 countries outside the U.S. From first launch of Hiberix in 1996 through 2008, approximately 55 million doses have been distributed. Studies of Hiberix have been conducted in Europe, Canada, and Latin America to support licensure in countries outside the U.S.

When considering Hiberix for approval in the United States, we reviewed the available clinical data and found that there were some limitations in the clinical studies, which had not been conducted under IMD. Some aspects of the clinical studies, such as priming history, dosing schedules, control vaccines, concomitant vaccines used, were not always consistent with current U.S. childhood vaccine recommendations.

Nevertheless, we found that the safety and effectiveness data from the available clinical studies were adequate to support accelerated approval of Hiberix for booster immunization against invasive Hiv disease. We viewed Hiberix as providing a meaningful therapeutic benefit over existing vaccines that were in short supply and the approval of Hiberix was subject to the requirement that the applicant study Hiberix further to verify clinical benefit.

In August 2009, Hiberix was approved for use as a booster dose in children 15 months through 4 years of age. The

indication is active immunization for the prevention of invasive Hib disease.

(Screen.)

Now, moving into the specifics of the pre-licensure safety data, in the Hiberix BLA there were seven booster immunization studies, in which a total of 1,008 children 15 to 18 months of age received a booster dose of Hiberix. In the booster immunization studies, there was not a control group of children who received a U.S.-licensed Hib vaccine.

The BLA also included two primary immunization studies of Hiberix, which were considered as supportive in the evaluation of Hiberix for booster immunization. Across the two primary immunization studies, nearly 1400 infants had received a primary series of three doses of Hiberix administered at three, four, and five to six months of age. In the primary immunization studies there were groups of infants who received U.S.-licensed control Hib conjugate vaccines, which were given as a primary series of either two or three doses depending on the vaccine.

(Screen.)

Safety monitoring in the clinical studies included parents recording daily on diary cards solicited local reactions and systemic adverse events that occurred within three to four days after vaccination. Unsolicited non-serious and serious adverse events were monitored for 30 days post-vaccination. Telephone follow-up to inquire about adverse events was conducted

during the first week post-vaccination, and study participants had follow-up visits at the study site, typically at about 30 days after vaccination.

(Screen.)

Beginning with the booster immunization studies, we'll go through a few slides on the safety data. There were no deaths among 1,008 toddlers who received a booster dose of Hiberix, which was administered concomitantly with U.S.-licensed Pediarix.

(Screen.)

Among 1,008 toddlers who received Hiberix and Pediarix, there were three non-fatal serious adverse events: accidental drug ingestion, pneumonia, and a case of gastroenteritis.

(Screen.)

This slide shows non-serious solicited adverse events that occurred within four days after receipt of Hiberix and Pediarix from one of the booster immunization studies -- local injection site reactions, pain, redness, and swelling at the Hiberix site -- as well as the solicited systemic adverse events -- fever, fussiness, loss of appetite, sleepiness. All occurred relatively commonly, 15 to 30 percent of participants.

Grade 3 solicited adverse events occurred in roughly 1 percent to 4 percent of participants, depending on the event.

Moving into the primary immunization studies --

(Screen.)

-- 2 of nearly 1400 infants who received three doses of

Hiberix and Pediatrix died during the study. There was a case of SIDS 18 days post-vaccination and an infant who died of a convulsive disorder of undetermined etiology 36 days post-vaccination.

Among the 4600 or so control infants, who received two doses of a control Hib vaccine licensed in the U.S. given concomitantly with Pediatrix, there were two deaths: a case of SIDS and a case of respiratory arrest 23 days after vaccination following seizures and sepsis.

(Screen.)

This slide summarizes all serious adverse events within 30 days post-vaccination in the primary immunization studies. It includes the fatal events on the previous slide as well as non-fatal serious adverse events. 2.2 percent of 1400 infants who received a primary series with Hiberix and 1.6 percent of 4600 infants who received a primary series of two or three doses of a control Hib vaccine experienced a serious adverse event. None of the serious adverse events following Hiberix was considered by the investigators to be related or possibly related to vaccination.

(Screen.)

The next slide will give a list of the serious adverse events that were reported in the 31 infants who had a primary series with Hiberix. The most commonly occurring serious adverse events were pneumonia, bronchitis, injury, pharyngitis, and viral infection. There were three cases of convulsions, including one

from a previous slide, in an infant who died 36 days post-vaccination. The convulsions were of undetermined etiology. There was a case of infantile spasms and then there was a case of suspected convulsions in an infant whose medical workup was negative.

Although not shown in this slide, there were also three cases of convulsions reported as serious adverse events in the control subjects.

There were three cases of dyspnea, three of gastroenteritis, and all of the other events listed on the slide occurred in one or two subjects.

(Screen.)

Now, at the time when the Hiberix biologics license application was submitted, the applicant had had substantial post-marketing safety surveillance experience with Hiberix in other countries and conducted a comprehensive review of the safety surveillance data that were available post-marketing, covering a 12-1/2 year period from June 1996 through November 2008. During that time, approximately 55 million doses of Hiberix had been distributed.

The ten most frequently reported events were pyrexia, a variety of local injection site reactions, crying, and administration error. Adverse events of special interest that may have an underlying autoimmune or hypersensitivity etiology included:

Three reports of leukocytoclastic vasculitis in infants.

Although review of those reports did not suggest a causal relationship with vaccination, because of the potential for an underlying autoimmune or hypersensitivity etiology the applicant closely monitors all reports of vasculitic syndromes following Hiberix.

There was one report of type III hypersensitivity in an adult who received Hiberix; and during this period there were 27 deaths, with a reporting rate of approximately 5 deaths per 10 million doses distributed.

At the bottom of the slide in the italicized text, there's just a note that in the period following the end of the reporting period until licensure of Hiberix, so roughly a 9-month period, there was one additional death reported.

(Screen.)

This slide summarizes clinical information on the 27 deaths that were reported in the period 1996 through November 2008. In 74 percent of the deaths, Hiberix had been administered with one or more other vaccines. In many cases these were vaccines that are not licensed in the U.S., including whole cell pertussis vaccine, as this was global post-marketing surveillance going back to 1996.

In eight of the deaths, the information available was insufficient for thorough review. Five were due to aspiration or respiratory tract obstruction. Five were due to acute infectious

processes. Four deaths occurred in infants with underlying congenital anomalies or concurrent conditions that were thought to contribute to death. Deaths were reported in twins who co-slept with their parents; etiology was unexplained. There was one death due to disturbance of ventilation in an infant found at autopsy to have multi-organ inflammation. One death occurred in an infant who was found to have hematologic abnormalities in spleen and bone marrow at autopsy, and there was one case of SIDS.

The one additional death reported from the end of the reporting period to the time of licensure of Hiberix was due to septic shock.

(Screen.)

So in conclusion, the available clinical data supported accelerated approval of Hiberix for booster immunization. Approval was subject to the requirement to study Hiberix further to confirm clinical benefit of booster immunization, as well as a requirement to complete an assessment of Hiberix in infants. There were no additional studies required to assess serious risk.

That concludes my presentation.

CHAIRMAN ROSENTHAL: Thank you.

Why don't we do -- do you have a preference as to whether we take questions at this point or whether we do questions at the end of both presentations? It may be best to do --

DR. MURPHY: Both people can stay until the completion?

DR. FARIZO: Sure.

CHAIRMAN ROSENTHAL: Okay. All right. Well, let's move ahead then with the next presentation then. If people can save their questions, we can take them all at the end.

So the next presentation regarding pediatric safety and utilization for Hiberix will be presented by Dr. Menschik. Dr. Menschik is a medical epidemiologist in the Vaccine Safety Branch of the Division of Epidemiology at FDA's Center for Biologics Evaluation and Research. Dr. Menschik attended medical school at Penn State and he completed his pediatrics residency at the University of Tennessee before working as a general pediatrician in private practice. He later received a master's in public health at Johns Hopkins University and completed a preventive medicine residency at Johns Hopkins University. Dr. Menschik has been with CBER since 2006.

Thank you for joining us today.

HIBERIX [HAEMOPHILUS B CONJUGATE VACCINE

(TETANUS TOXOID CONJUGATE)]

PEDIATRIC SAFETY AND UTILIZATION REVIEW

(Screen.)

DR. MENSCHIK: Thank you. Good morning and thank you for the opportunity to present today. I'm going to present a pediatric safety review for Hiberix, which, as you've just heard, is a haemophilus influenza b vaccine approved for use as a booster dose in children age 15 months through 4 years.

(Screen.)

I'd like to begin with this slide from the referenced MMWR article illustrating the public health impact of Hib vaccination. Before the availability of Hib vaccine in the U.S., invasive Hib was a leading cause of several serious and some potentially lethal diseases, including meningitis and epiglottitis. Over the course of the decade following the introduction of conjugate Hib vaccine, the annual incidence of haemophilus influenza invasive disease in children less than 5 years old declined dramatically, as indicated by the red line.

The embedded graph in the upper left portion of the figure highlights the relatively low and unchanged incidence, less than one per 100,000, of haemophilus influenza invasive disease over time in children five years of age and older.

(Screen.)

Now I'd like to focus specifically on Hiberix. As you've just heard in the last presentation, Hiberix is indicated for active immunization as a booster dose in children 15 months through 4 years of age for the prevention of invasive disease caused by Hib. I'm now going to present a review of post-marketing pediatric safety in the year following U.S. licensure of Hiberix.

(Screen.)

Prior to U.S. licensure, the sponsor identified three adverse events, based on global post-marketing safety experience, that would have post-licensure expedited reporting and enhanced

surveillance, death, leukocytoclastic vasculitis, and type III hypersensitivity reactions, which were discussed during the last presentation. Since U.S. licensure, no cases of leukocytoclastic vasculitis or type III hypersensitivity reactions were identified.

(Screen.)

Since U.S. licensure, there was one labeling change related to safety. The text shown was added to the warnings and precautions section to indicate that tip caps of the prefilled syringes may contain natural rubber latex. Previously the label had stated that the tip caps did not contain latex. The label change was not prompted by any adverse events related to latex allergic reaction after Hiberix.

(Screen.)

In the year following U.S. licensure of Hiberix, about 2.8 million doses were distributed in the United States. Unfortunately, no data are available to comment on what proportion of these doses were administered at different ages.

(Screen.)

This table summarizes adverse events reported to VAERS after administration of Hiberix in the first year after its FDA approval. Overall, there were about as many foreign reports as domestic reports, with far more foreign reports in children under 15 months. The light blue band shows events in the approved age range, with U.S. reports circled in red. There were two U.S. serious adverse events reported in the approved age, one of which

was a death by autopsy-confirmed homicide.

U.S. reports to VAERS are summarized on the next slide.

(Screen.)

The vast majority of Hiberix vaccinations, more than 90 percent, were given with at least one other vaccination. There were three reported serious adverse events, including one death that will be described in the following slide. The ten most commonly reported adverse events are listed on the slide in the order of descending frequency. As you can see, the majority of terms refer to local reactions.

(Screen.)

Here's a description of the three reported domestic serious adverse events after Hiberix. Case one is a 21-month-old girl who developed signs and symptoms of an allergic reaction shortly after vaccination. She was admitted for observation, subsequently improved, and was discharged with a diagnosis of penicillin allergy.

Case two is a six-month-old boy who developed signs of sepsis with acute liver failure one to two days after receiving Hiberix. He was hospitalized, treated with IV antibiotics, and discharged home after gradual improvement.

Case three is a two year old girl who died of inflicted head trauma, with the manner of death classified as homicide in the medical examiner's autopsy report.

(Screen.)

So this completes the one-year post-approval pediatric safety review for Hiberix. No new safety concerns were identified during the course of this safety review. We recommend continued monitoring of VAERS for new safety signals. Does the advisory committee concur?

(Screen.)

I'd like to acknowledge and thank all the people named on this slide and any I've neglected to name for their contributions to the presentation. Thank you.

DR. MURPHY: David, just before you leave, and again because we have so many new members here today or participants, would you also summarize for them in a few sentences how the normal routine monitoring for vaccines occurs, because it's really quite different and involves the CDC and others? Could you just give the committee a sentence or two on that?

DR. MENSCHIK: Sure. Our primary tool is VAERS, which is passive surveillance data, spontaneous reports that come from all sources. We have surveillance reports that we do at regular intervals. For new products we do them on a monthly basis. And they have a variety of components, but it's generally based on VAERS unless there's a specific concern. In some cases for other vaccines, vaccine safety data link is another source, which is run by CDC.

Is that helpful?

DR. MURPHY: I just wanted to make sure the committee

knew that they work with CDC also in a routine manner in looking at vaccine adverse events.

DR. MARTIN: I'd just like to add that that routine monitoring involves looking at VAERS, so looking at the individual adverse reports. Then, as David was saying, that data is aggregated for new products on a monthly basis, for other vaccine products on a quarterly or semi-annual or annual basis. And then we also apply data mining algorithms to that aggregated data, and the medical officers also review the pertinent literature and any pertinent submissions from the sponsors.

CHAIRMAN ROSENTHAL: Do you mind introducing yourself?

DR. MARTIN: Sorry. I'm David Martin. I'm the Acting Division of Epidemiology Director within the Center for Biologics.

CHAIRMAN ROSENTHAL: Thank you very much.

All right, thank you for those presentations on the pediatric safety review for Hiberix. This is now the time for the committee to ask questions or to discuss this. Dr. Shwayder, you're leaning forward towards the microphone.

DR. SHWAYDER: We all have hot-button issues in our practice and I'm fully in favor of vaccinating any and every kid for everything we have. I think it's so important for our public health, for the safety of our country, and I really marvel at your statistics and I just support it, and I think we should continue what you're doing. I agree with the summary conclusions.

CHAIRMAN ROSENTHAL: Thank you.

Yes, Dr. Rogol?

DR. ROGOL: A quick question. In the first talk, 5 per 10 million deaths. What is it in the general population? Is that par for the course? I just don't know the data.

DR. FARIZO: These are global reports, so much higher expected death rate.

DR. SHWAYDER: Which is much, much higher, the background scatter?

DR. FARIZO: I'm sorry. The general background rate of deaths in infants globally would be much higher than what was observed with Hiberix post-licensure.

DR. ROGOL: I was thinking U.S. and I just didn't know. But if you think of Africa and Haiti and a few places like that, yes. Thank you.

CHAIRMAN ROSENTHAL: Dr. Romero and then Dr. Bhatia.

DR. ROMERO: I was wondering -- it may not be possible. Could you give us a little more detail if there's any information regarding the etiologies of the sepsis cases and the pneumonia cases that were reported? Again, I understand that that may not be available.

DR. FARIZO: We have fairly limited detail on those cases. You know, as I mentioned, I think part of the limitations in the detail reflects the fact that these studies were not done under -- for the clinical studies, were not done under INDs. So we didn't have an ongoing clinical development program for

Hiberix, so in many of the cases we had just limited information.

So I don't have specific organisms and so on.

DR. ROMERO: Not to be veiled about the question, but the reason why is, is there a precedent or is there a tendency to have greater infections due to Hib following the vaccine? That's the reason for asking the question.

DR. FARIZO: I think that question came up in sort of the dawn of use of Hib vaccines, and I believe the evidence over time was against an increased risk of infection following vaccination.

DR. ROMERO: Right. And if it doesn't show -- I'm an old man; I remember the vaccine coming out and those questions coming up.

CHAIRMAN ROSENTHAL: Dr. Bhatia?

DR. BHATIA: Just to answer Dr. Rogol's question, worldwide I think the infant and early childhood mortality is upwards of 15 per 100,000, and that's why it's one of the Millennium Development goals to reduce mortality.

CHAIRMAN ROSENTHAL: Doctors Anderson and then Motil, and then Dr. Wagener.

DR. ANDERSON: The question was more for curiosity: Does your surveillance data allow you to separate out when the patients are taking, are exposed to more than one vaccine at a time? I think the statistic I saw was 74 percent had multiple vaccines.

DR. MENSCHIK: It's actually much higher. It was about 90 percent in the post-marketing setting that had concomitant vaccinations.

DR. ANDERSON: Are you able to parse out the SAEs and attribute those?

DR. MENSCHIK: Not -- generally, not neatly. We do have tools that help to separate out, such as data mining, which is kind of viewed to be outside the scope of this, but I can just tell you that there were no data mining signals specific to this product.

CHAIRMAN ROSENTHAL: Dr. Motil?

DR. MOTIL: My question rather parallels Dr. Romero's in the safety assessment. Specifically, some of those unusual infections; did anyone ever mention haemophilus influenza as an etiology, for those of us who remember the old days of that infection?

DR. FARIZO: I think there were some cases of what would have been called -- picked up as a vaccine failure in the global post-marketing safety surveillance. I don't have the details on the top of my head, but with that many doses distributed you will get some cases -- some of the cases of haemophilus influenza type B disease in infants who were not fully vaccinated, so they may have received one dose or not a full series.

CHAIRMAN ROSENTHAL: Dr. Wagener, you had your hand up.

DR. WAGENER: As I understand the data, about 45 percent

of current utilization is what we would call off label. My question would be, do you know or can you divulge whether or not the company plans on having this approved at some point as a primary vaccine instead of just a booster shot? And if that's the case, will that involve things such as antibody levels and monitoring for efficacy?

DR. MENSCHIK: I think that's a question more for the product --

DR. FARIZO: I can address the latter part of the question or your comment that it looked like 45 percent was off label use. I don't quite understand what --

DR. WAGENER: That was based on his data where 55 percent of the cases were in the blue area, which was the labeled area, and 45 percent were either in a younger age group or in the older.

CHAIRMAN ROSENTHAL: Can we go back to that slide?

(Screen.)

DR. MENSCHIK: Those are actually raw numbers of adverse events reports to the VAERS system. So those don't reflect utilization patterns per se in a direct fashion. In other words, if you go to Slide 6, that's essentially what we know at the agency, is we just know that there was 2.8 million doses distributed. But we can't tell you specifically how many of those were used in an off-label fashion.

DR. WAGENER: Right. I guess that would be if you

assumed that the adverse events are different in different age groups, which they very likely would be, I understand.

DR. MARTIN: We understand. It's just that we can't tell you with certainty.

DR. FARIZO: Regarding primary immunization with Hiberix, under the Pediatric Research Equity Act approval was contingent upon a requirement to study Hiberix in infants for primary immunization. In any study of a new Hib vaccine, we would require effectiveness data as well. So there will be -- the requirement would be to conduct a controlled study for safety and effectiveness based on immune response.

Although I did not present the effectiveness part of the pre-licensure data, the pre-licensure data for Hiberix that supported approval for booster did also include effectiveness data.

CHAIRMAN ROSENTHAL: Can we go to the last slide, please.

(Screen.)

CHAIRMAN ROSENTHAL: So now the question is, unless there are other questions or discussion, other discussion or other comments, then we'll go ahead and vote. Does the committee concur that the FDA should continue routine monitoring through the VAERS system for new safety signal related to Hiberix? All in favor?

(A show of hands.)

CHAIRMAN ROSENTHAL: Thank you. Any opposed?

(No response.)

CHAIRMAN ROSENTHAL: I see no hands in opposition. Dr. Rogol, would you start us?

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener, yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Concur.

DR. ANDERSON: Garnet Anderson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: Okay, great. Thank you.

So let's move right along to the discussion of Intuniv, and Dr. Sachs will be presenting a safety review of adverse events for Intuniv.

Dr. Sachs is a team leader in the Pediatric and Maternal Health Staff in the Office of New Drugs. She's been with the FDA since 2002 as a member of the Pediatrics Group. She graduated from the University of Maryland School of Medicine and completed her internship and residency at Children's Hospital-National Medical

Center. She's been practicing as a pediatrician for over 20 years and she continues to see patients.

Dr. Sachs.

INTUNIV (GUANFACINE HYDROCHLORIDE):

STANDARD REVIEW OF ADVERSE EVENTS

(Screen.)

DR. SACHS: Good morning, everybody. It's nice to see some familiar faces, and I hope you can hear me okay. Please let me know if you can't.

This is the pediatric-focused safety review for Intuniv.

(Screen.)

Whoa. Sorry about that.

(Screen.)

So I will be first talking about giving you some background information about the drug product, describing very briefly the pediatric studies that led to the approval, and the labeling changes related to them. I'll also review some of the safety labeling that's real important as you're looking at the adverse events, describe the drug use trends, and then talk about the adverse events, including some additional information on some prior OSE reviews so you can really have some context, and then summarize it all for you.

(Screen.)

Speaking as a pediatrician, as you guys know, guanfacine has been used off-label for years, so this approval of Intuniv is

an extended release tablet that's approved for the treatment of ADHD both as monotherapy and as adjunctive therapy in pediatric patients ages 6 to 17. Although safety and effectiveness has not been established for the younger age group and efficacy has really not been studied yet past nine weeks, we are going to be gathering some additional data on that.

(Screen.)

This selective 2-alpha adrenergic receptor agonist is marketed by Shire.

You all may know that guanfacine was originally approved as an immediate release product marketed as Tenex, approved for hypertension in patients 12 years and older, and in the XR formulation just was approved in 2009 for monotherapy, and then subsequently in February of this year for the adjunctive therapy.

(Screen.)

The approval of the monotherapy regimen triggered PREA because it was a new dosing form as well as indication and had a new dosing regimen. As part of the approval, there also are some additional post-marketing studies that will be done. One is to look at the long-term efficacy and maintenance and safety for all the age groups. One was an efficacy study focused primarily on adolescents, and the last one is an adjunctive therapy study with psychostimulants, and that actually has been fulfilled with this labeling change most recently in February.

(Screen.)

So here's some information about the pivotal efficacy studies that were performed. These are the ones that establish efficacy for monotherapy, and they included two fixed-dose, double-blind, placebo-controlled trials. One was in doses ranging from 2 to 4 milligrams in about 345 patients, and the second trial was with doses from 1 to 4 milligrams in 324 patients for a slightly longer period of time.

In both trials, after randomization the dose could be titrated in increments of about 1 milligram per week. The 1-milligram dose was assigned only to patients that were less than 50 kilos or 110 pounds, and patients who weighed less than 25 kilos, or 55 pounds, were not included in either study. That's about the average weight of a 7 year old boy and a 7-1/2 year old girl.

(Screen.)

One slide back, sorry.

(Screen.)

I'm used to doing this with two monitors, so forgive me.

So the efficacy was established in the pivotal study based on clinically and statistically significant reductions in the ADHD rating scale, as well as subscales of inattention and impulsivity. The efficacy was both dose and exposure-related.

An analysis by age and gender revealed that there was no differential response on gender, but, although we did see the treatment effect in the younger age cohort, the adolescents did

not seem to experience that. Part of the reason for this is that there was a relatively small number of adolescents in the study. Proportionally, it's only 25 percent of the overall study. Many of them may have received sub-optimal doses just because they were randomized to a fixed dose initially.

(Screen.)

But nonetheless, at this point we did get full product labeling for Intuniv for the monotherapy.

(Screen.)

Now, actually this is the adjuvants study, and I just want to talk about it really quickly so that you have additional safety that adolescents can be treated. This was a flexible dose, double-blind study where patients were titrated to an optimal dose. This was a fairly large study also, about 450 patients. These patients, they got randomized to the dose of the Intuniv and then were titrated to their dose, maintained on that stable dose for three weeks.

(Screen.)

As you can see, there was a pretty broad range of allowable concomitant psychostimulants, and these included the Adderall products as well as a good broad range of methylphenidate products.

This trial as well showed statistically significant improvement in the ADHD rating scale, and the labeling was subsequently updated in February to allow for the adjunctive

indication for the concomitant use of guanfacine with psychostimulants.

(Screen.)

So I would like to, if you'll excuse the pun, focus your attention on the safety labeling. The warnings and precautions section does outline some important cardiovascular and CNS side effects, as well as a warning not to use the product concomitantly with other guanfacine products.

You can see that for hypertension, bradycardia, and syncope the adverse events are pretty much dose-dependent and there's about 7 percent hypotension in the Intuniv group compared to the placebo group, about twice the rates.

For sedation and somnolence, the rates can be pretty high with monotherapy, almost up to 40 percent in patients versus Intuniv and 20 percent for patients in monotherapy, and again this does exceed the rate for patients that were being treated with placebo.

(Screen.)

So we can look at the adverse events in context. Here's some information about the use. For a pediatric product this has fairly significant use. Of the total 2 million guanfacine prescriptions that were dispensed, about 67 percent were generics and about 33 percent are Intuniv, so about 600,000—so. If you look at unique patients that received a prescription for any guanfacine product, there's about 476,000.

(Screen.)

If we break it down a little further for you, if you look at those total 2 million guanfacine and then focus on the ones that got the Intuniv, the 676,000, again most of them are focused on the 6 to 12 year old age group. About 25 percent were adolescents, kind of what you saw in the studies for the products. Less than 5 percent were for either patients less than 5 or adults. Again, if we look at just the unique patients you see the same pattern.

(Screen.)

This slide just shows us that the use of Intuniv has been increasing since the year after approval. I could actually superimpose the use slide for guanfacine on this total. So the increase in use for all guanfacine products over the year has been primarily associated with this increase in Intuniv prescriptions.

You can see the pattern again, where it's mostly in the 6 to 12-year olds, and then the adolescents, and then -- that's my shadow -- less than 5 percent in the adults and the kids under 1.

(Screen.)

Not surprisingly, the type prescribers for this product are psychiatrists and pediatricians, and the top diagnosis code is ADHD.

(Screen.)

So just so you have a little more context, we did focus the review on just the one year since the approval of Intuniv, but

that doesn't mean that we haven't looked at guanfacine safety in kids for a long time. So initially in June of 2000, there was a completed review to look at use in pediatric and adolescent populations with ADHD. At that time, the most frequent adverse events in pediatric patients were characterized: the CNS disorders, which does include some convulsions as well as the sedation you heard about; some psychiatric disorders; mania; cardiac disorders, mainly the bradycardia; and injuries and poisonings related to overdose.

(Screen.)

In August of 2000, in part in preparation I think for an advisory committee looking at sudden death and serious cardiovascular events associated with psychostimulants, they looked at the use of guanfacine with other psychostimulants and there was no serious adverse events identified.

(Screen.)

In April of 2001, there was a review of mania and aggressive behavior, prompted in part by a case series from a single center of these reports, and the labeling for the guanfacine IR product was updated to reflect the post-marketing adverse events of mania and aggression, with a caveat that these events were seen in a single center in patients who had family history or other clinical history that might predispose them to mania.

(Screen.)

Finally, in preparation for the NDA approval, an overall review of adverse events for the guanfacine was done and there was no new signals identified. It did confirm the syncope signal that was seen in the trials.

(Screen.)

Okay. So with that backdrop, let's look at the one-year post-marketing product-focused safety review for Intuniv. In this case what we did was we looked at the 79 adverse events total since the product has been approved, and that's because there's a large number of null reports. So a hands-on review was done for all the 79 cases.

(Screen.)

This slide shows you how we came up with the final case series. So once duplicates were removed and patients that were just totally adults were excluded, patients that had non-serious outcomes or reports where there was not an age indicated at all, we ended up with 47 cases and 2 fatalities.

(Screen.)

If you look at the demographics real quickly for the reports of the 47 cases, you can see there's a male predominance.

Again, most of them focused in the middle age group, and the mean doses, with one exception, actually are within the approved dosing.

(Screen.)

So let's talk about the two fatalities real quickly.

One was a 9 year old boy who experienced sudden death 6 days after he started guanfacine XR. Unfortunately, he had missed three days of his medicines, which included seizure medications, and was found dead in his bed. At post-mortem his levels of drug were sub-therapeutic and the autopsy did report his cause of death as sudden unexpected death in epilepsy.

(Screen.)

The second fatality was a 16 year old who took an unknown dose of guanfacine XR and was probably -- I'm sorry?

DR. SHWAYDER: Okay, I'm with you.

DR. SACHS: And unfortunately had taken probably some multiple medications, as his post-mortem tox was positive for multiple medicines, and his death seemed to be related to the drug interactions between them all.

(Screen.)

So now we'll talk about the non-fatal adverse events that were associated with the product. There's 45 cases in all and we've categorized them into the general categories of syncope, cardiovascular, neurologic, psychiatric, and miscellaneous. And because several of the reports did include gastrointestinal reports, I'll talk about that as well.

Just remember as you're thinking about these cases that each case could describe adverse event. So from now on if you want to add the numbers, they're not going to add up.

So the syncopal events, these 17 cases, syncope is well-

labeled. Again, it's the male predominance, in the approved age range and the approved dosing. Of the few cases that reported the time of onset, it was mostly within the first month of therapy, usually within the first week or so.

Four cases did report concomitant meds that are also labeled for syncope and syncope is well spelled out in the warnings and precautions.

(Screen.)

If we look at the cardiovascular adverse events, these also are labeled: bradycardia, arrhythmia, QT prolongation and hypotension. Again, a male predominance. The age group is in 4 to 15, and the dose is in the approved range. There were potential contributing factors in two of the cases. The QT prolongation case was associated with congenital QT prolongation by history. In one of the other -- in one of the cases of bradycardia, the patient also took another medicine labeled for bradycardia. Nonetheless, labeling does spell out in warnings and precautions bradycardia and hypotension, and the clinical trials section of labeling does go on to describe the effects on heart rate and QT interval in a thorough QT study that was done in adults that did show a dose-dependent increase in QT, although the clinical significance does not seem to be there.

(Screen.)

I'm looking at the ten cases of neurological events. Again, it's the male predominance, at fairly standard doses. In

this case we did some unlabeled events. The labeled events included seizures, somnolence, and headache, which are described both in the warnings and precautions section as well as the clinical trial experience, and one of the reasons for discontinuation.

Looking at the unlabeled events, there were three patients that were unresponsive to stimuli. Two of those happened to be post-ictal. The other one was a patient who was started initially on 3 milligrams without any titration, experienced hypotension with a blood pressure of 50 over 20, and then became unresponsive. But the primary key in that report was unresponsive to stimuli.

Then there were two cases that muscle twitching was associated with and one patient the had some dyskinesia, and other factors also may have contributed to these reports, either underlying cerebral palsy or seizure disorder.

(Screen.)

Looking at the psychiatric adverse events, again we see a male predominance. The age is fairly typical, and here's where you saw the higher dose. One of the patients had an overdose. The events occurred within generally 40 days of therapy and mostly the reason for use was the approved indication. One patient did receive it for hyperactivity, aggression, and opposition.

(Screen.)

Labeled psychiatric events are agitation, anxiety,

irritability, and nightmare, and these are well described in the clinical trial experience. Sleep terror is not technically described, but I think we can agree it's fairly closely related to nightmare.

(Screen.)

Looking at the unlabeled events, there were two patients that had some aggression and both the patients were possibly -- were on medications that are also labeled for aggression. There was two patients that had an intentional overdose that was not clearly associated with suicidality, meaning that there was no suicidality described in the report: a 15 year old male who took several -- who an hour after taking his first dose decided it wasn't working, so he took the remaining 21 milligrams, and he became understandably anxious, agitated, and angry and was seen in the ER. His symptoms resolved and he gradually was titrated and became stable on 4 milligrams.

Then there was a 15 year old who took a handful of guanfacine and she experienced nausea, dizziness, and five episodes of syncope and had to be treated with IV hospitalization -- IV fluids and hospitalization.

(Screen.)

There were two events associated with suicidality. One was an 8 year old who had been stable on 1 milligram for a month. The dose was increased to 2. She threatened to kill herself and others, but was actually able to be maintained on that dose and

the event resolved without any intervention.

The second case associated with suicidality was in a 12 year old who was participating in a placebo-controlled dose optimization trial, and she became upset because she lost her cell phone and Facebook privileges. Tell me about it. Anyway, the study drug was titrated down, she was withdrawn from the study and the adverse event resolved. But from the report actually we can't tell whether she received the Intuniv product or had gotten placebo.

(Screen.)

Lastly, there were single reports of visual hallucinations, impulsive behavior, and mania. Now, you may remember I mentioned that GI complaints were prominent in six cases. GI complaints are actually labeled, but these events you can see on the slide -- abdominal pain, decreased appetite, vomiting.

(Screen.)

The final events were in the miscellaneous category and both happened to be in 10 year olds. One was a patient who had a rash and then the other one was a patient who complained that her insurance company made them substitute the IR product for the XR.

(Screen.)

So this concludes the pediatric-focused safety review. No new safety signals were identified. Labeling has been changed where we now have a monotherapy and an adjunctive therapy

indication, and we recommend continued routine monitoring, which in this case means you likely will hear about them again since the assessments when they come in from the post-marketing studies will trigger another safety review. Does the committee concur?

(Screen.)

Before you all talk about it, I'd just like to thank a lot of folks who contributed to the presentation.

CHAIRMAN ROSENTHAL: Thank you, Dr. Sachs, for your presentation.

Dr. Bhatia, I saw your hand go up.

DR. SACHS: Before you ask the question, I just want to make sure you guys see -- I think it's Mitch Mathis over there from the Review Division, and Dr. Loughran. You might want to introduce yourselves.

CHAIRMAN ROSENTHAL: Yes. Yes, please, if you will.

DR. LOUGHRAN: I'm Tom Loughran. I'm the Director of the Psychiatry Products Division.

DR. MATHIS: Mitch Mathis, Deputy Director.

CHAIRMAN ROSENTHAL: Thank you very much for joining us at the table.

Dr. Bhatia.

DR. BHATIA: Thank you for that. I just have a question for clarification. A lot of the AEs had concomitant drug therapies. Do we have any information on possible or actual drug-drug interactions from this group of patients?

DR. SACHS: The labeling does actually have some information about drug-drug interactions, and if you can give me a second I can look. I don't believe there are any big ones. I think there is certainly some labeling, for example, if you had another product that's known to cause hypotension you'd be a little careful with the two combined.

DR. McMAHON: In our presentation and in our review we tried to highlight when we were talking about an adverse event that was also in the label of the concomitant medication that was mentioned. But as far as drug-drug interactions, AERS is not really the best place to be able to learn a lot about drug-drug interactions. It's something that we descriptively talk about in our reviews.

CHAIRMAN ROSENTHAL: Dr. Reed, were you going to add something else to that question or were you just affirming that that was your question as well?

DR. REED: I was affirming that that was my question, particularly related to this drug. Knowing how many medications go through the 3A4 and in pediatric practice this drug I would say is probably one a little off the radar screen, particularly relative to drug interactions, and the side effects could be relatively substantial if you had marked prolonged accumulation. So I was agreeing.

DR. SACHS: So the labeling does actually have a section about drug interactions, which outlines the SIP 3A4 inhibitors and

inducers, as well as co-administration with valproic acid, anti-hypertensive drugs, CNS depressant drugs, and oral methylphenidate as well as lisdexamfetamine.

DR. LOUGHRAN: This is Tom Loughran. Right, the most important interaction is the 3A interaction, and it's very prominent in labeling. If you notice, in the highlights section it's the first one mentioned, both with inhibitors and with inducers, which can decrease the levels of guanfacine.

CHAIRMAN ROSENTHAL: Dr. Towbin.

DR. TOWBIN: Well, I appreciate this review. Indeed, this is a drug that's seen a very dramatic increase in use. I appreciate the comment related to the cytochrome system, and the label is I think a fairly generic one. The concern that I would have about this is the concomitant administration of drugs for anxiety or depression, serotonin reuptake inhibitors, particularly with this agent, and I was wondering whether there was any latitude to increase some of the names or examples that are given in the label that talk about 3A4 inhibition. A little later we'll talk about Citalopram and that's an example of one of those drugs that might be given the comorbidity with anxiety and depression in this group that has ADHD, is not infrequent.

So one would worry about people just passing that by a little too quickly. So that would be one thing that I would wonder about.

Then I guess the other, which is a separate question, if

I'm not piling on too much, but these studies, of course, were all done in populations that would exclude individuals with developmental disorders, and I was wondering whether there was any consideration to how the use review going forward might break that population out, where one would be concerned about a higher risk of ill effects, adverse reactions, and so on, whether there's a way in which that can be followed prospectively so that we might hear about that in the future.

DR. LOUGHRAN: I can respond to the question about expanding the labeling to mention some other 3A4 inhibitors. It was studied with ketoconazole, the most potent inhibitor, and there was about a threefold increase in guanfacine level. So it is a reasonable question. We'll take that back and see if we can't expand that a little bit.

On the other, on the use question, I think someone else needs to respond to that.

DR. McMAHON: Yes. Again, I'll ask whether anyone specifically for the drug use team is here? I think not.

Oh, good. Okay. I'd really like it if maybe you could respond. Do you want to maybe use that microphone there?

CHAIRMAN ROSENTHAL: Please come up to the table.

You prefer that she use the mike at the table? If you will, please introduce yourself.

DR. MEHTA: Hi. I'm Hina Mehta, Acting Drug Use Team Leader. Sorry, can you repeat the question?

DR. TOWBIN: My question related to, in these studies individuals with developmental disorders of all kinds are routinely excluded, and since problems with inattention, distractability, and hyperactivity are very commonly seen in the population of individuals with developmental disorders, I was wondering if going forward there would be a way to break that information out so that we could see how much that was -- this drug was being used in that population, and to be able to monitor the risks and side effects in that more, if you will, side effect-prone population, more vulnerable population.

DR. MEHTA: The only use available we have is by a diagnosis, which is actually from a survey of physicians, and we really can't break down much information, anything further than that. But other usage is just general use and includes all types of patients.

DR. McMAHON: I'm not sure if you're also asking about adverse events in sub-populations, because that we can look for. It's not usually easy to find, depending on what the sub-population is, but we can do things like hex-string searches in AERS to look for particular sub-populations and things like that, and compare sub-populations in AERS to maybe overall populations within that same age group or something.

But that isn't necessarily going to give you a very robust answer to the question. I'm not sure that it would -- again, a descriptive analysis that we could probably do in AERS

doesn't give you a denominator.

DR. TOWBIN: So I guess the reason that I would want this information known or to consider our being able to review in the future is that I would be afraid that people might generalize from this data in what is an otherwise healthy population to individuals who have more serious kinds of developmental problems.

One would just like the practicing community to have that information available to it, and if there is a signal there may be an elevated rate in adverse events or ill effects in that sub-population one would want to know that.

This problem, that is the symptoms for which this drug is given, is much more common in that population. So you have this odd situation where a population that shows the symptoms very prominently isn't studied and you have the data in a population that may not generalize to that more developmentally disordered one, if I'm making myself clear.

CHAIRMAN ROSENTHAL: Yes, Dr. Rakowsky?

DR. RAKOWSKY: Thank you, Dr. Sachs, for a nice presentation. Just a follow-up to Dr. Towbin's question. In the use utilization, we do have the diagnosis for which this was prescribed. Is there a way to find concomitant medication use as well, to start to tease out some of the concerns that Ken has?

DR. SACHS: Yes. We do have -- we are able to do analysis based on concomitant medications. We did not do it for this review, but we could if that's requested.

CHAIRMAN ROSENTHAL: So I think this is an important point that's being discussed, that often the approval process relies on studies from populations without significant comorbidities, and following the approval process the medications are used in populations with comorbidities, and that it can be hard after the fact to go back and explore whether those sub-populations with specific comorbidities are at greater risk for adverse events.

So if there are ways to go back and explore it using concurrent medication use or other mechanisms that you have at your disposal, that's -- would people be in favor in this particular case of recommending such a further assessment? Yes?

DR. MARTINEZ ROGERS: I just want to add one question. I'm wondering if you look at if the adverse reactions were different for the majority population versus any ethnic, racial groups?

DR. McMAHON: We don't have information in AERS on race.

CHAIRMAN ROSENTHAL: Dr. Towbin?

DR. TOWBIN: While we're on this, one would also expect to see very high rates of co-administration of atypical antipsychotics with this agent and effects on cardiovascular, blood pressure, and conduction changes would be another thing that one would want to look at, the blood pressure changes in particular.

CHAIRMAN ROSENTHAL: Dr. Murphy, do you have any comment

on the direction that the discussion is going?

DR. MURPHY: Just whether I have it correctly summarized. So what we want is the committee would like us to come back to them with a look at what use is by sub-population, by indication basically, by indication, which you think you can sort through some of that; is that correct?

DR. SACHS: I thought it was by with concomitant medication.

DR. MURPHY: Well, that's the second thing. There's two things going on here. I think the committee wants to know what -- at least I've written down, to look at the use in a population that has developmental delay, so using the diagnosis. You can do that?

DR. SACHS: The only diagnosis which was in the background package --

DR. MURPHY: We're talking about for future, for future analysis.

DR. SACHS: The only diagnosis information we have is what was already in the background package. And it was broken down by age.

CHAIRMAN ROSENTHAL: So it was my sense, while we're sorting this out, it was my sense that it would be hard using diagnostic codes to go back and understand whether there are children with specific comorbidities that might be at greater risk for adverse events. It would be difficult to do that directly,

but there might be a way that we could get to it through the back door by looking at concomitant medication use.

DR. MURPHY: Okay. So I guess we can also look at this list and pick out -- see, we can go in and pick out the things on this list we think would be relevant to maybe this developmental delay population.

CHAIRMAN ROSENTHAL: And the list that you're holding up is? Can you describe it?

DR. MURPHY: The list that is the diagnosis associated with the total number of uses, okay. So in here we have to go through and pull out -- there are -- I just saw it -- behavioral. There's -- but I don't see, just quickly looking at this, a way to get at some of the kids who have these developmental delays.

So we'd have to come up with the diagnostic codes that we think we would be interested in.

DR. SACHS: The other thing, if I may add, that at least I'm hearing is that if, for whatever reason, we would be considering doing a written request for this product, we would probably need to look at the population of developmentally delayed individuals if that offered a public health benefit to do so. And I don't know if the company has submitted a PBS or anything, but that is something that we can take back.

DR. MURPHY: And we had a sidebar discussion here that we want to look at the use. I guess we'd like to see if we can hone in on the use, and what at committee is asking is that --

there are two things. They want us to try to get at where it's being used in other populations, particularly those kids who might have more adverse events because they're -- two things: they have other diagnostic entities that may be associated with their primary diagnosis; and then secondly, they're on other concomitant meds, and that all of these meds, many of them, tend to use the same pathway.

So is there a way to come in and get a look at concomitant meds that we think are particularly prone to use this pathway, and then also look at the use by diagnoses. We'd have to come up with some better diagnostic codes.

Then, Tom, did you want to say something else?

DR. LOUGHRAN: Yes. I just wanted to, in terms of the written request, we've already issued a written request for this drug, that's focused primarily on getting better data on adolescents, since that was the question from the monotherapy studies. So we're not going to be able to handle this through the written request mechanism.

DR. MURPHY: So that was a long-winded way of saying we don't have a button we can go to and push, but we can maybe sit down and analyze what sort of codes and what sort of concomitant meds we'd be particularly interested in, go in and ask those questions of the use, and then also do an adverse event review, and bring that back to the committee.

Is that -- did you summarize that at all?

DR. TOWBIN: As usual, Dr. Murphy, you've taken my obtuse comments and brought clarity and illumination to them.

CHAIRMAN ROSENTHAL: So you know, I would just add that, although we're talking about Intuniv, that this issue probably pertains to many of the medications that are prescribed for children with psychiatric and behavioral disorders, and that it may be an issue that is worth broader consideration with the agency.

I know that you guys think about these things, but this seems in the practice of medicine to be increasingly a common issue, where children with psychiatric or behavioral disorders and comorbidities are subjects in polypharmacy, N of one trials, and if there is some data that we can glean from the data that the agency has access to around whether this represents a practice or if there are ways that we can make these practices safer, then that would be useful in a public health context as well.

DR. MURPHY: I think Tom had already said that they're going to look at potentially expanding the list of some of the concomitant meds, and that might get to that issue also.

DR. LOUGHRAN: Right. It would be helpful to have additional data to support that, and so whatever we can do to explore existing databases to get better information on concomitant use would be helpful in making labeling changes.

CHAIRMAN ROSENTHAL: Yes, Dr. Towbin?

DR. TOWBIN: Then of course, since these symptoms don't

arise de novo at age seven, the other thing that I'll be very interested in as we go forward is looking at the use of this in children who are four to seven. I think many people are reluctant to give this particular agent to individuals under four, but the problems of hyperactivity and impulsiveness are very commonly observed in that kind of pre-school age group and I would expect that we'll see an increase from the rates that were described here. Again, I think in these kinds of dose forms we may see kind of higher risks for those individuals.

CHAIRMAN ROSENTHAL: Dr. Motil?

DR. MOTIL: Just one other comment. In the real world of GI practice, I find that the number of GI complaints, symptoms, concomitant issues that were reported to be rather low. Again, in this population the kinds of issues that we see in addition to behavioral and psychiatric issues are always related to GI symptoms of significant magnitude and appetite issues that may or may not, again, be drug-related.

So I guess I would encourage those kinds of considerations in exploring and reviewing your data base.

DR. SACHS: Tom, correct me if I'm misspeaking, but now that you've mentioned we're doing this study, isn't growth part of it?

DR. LOUGHRAN: Can you clarify, part of what?

DR. SACHS: Part of the follow-up studies that are being required. Isn't monitoring growth for maintenance one of the

components?

DR. LOUGHRAN: It hasn't been a requirement to do that. It wasn't a post-marketing requirement. It's very difficult to look at growth long-term without a control group, and the challenge is having a study where you have an adequate control group, because the illnesses themselves that we're dealing with sometimes have growth effects. So it's a great challenge.

We didn't make that a requirement, to look at long-term growth effects. In the short-term trials, we didn't see any real effects on weight.

CHAIRMAN ROSENTHAL: Dr. McMahon, were you going to add something?

DR. McMAHON: I was -- if I was understanding the comment, the previous comment about GI symptoms correctly, I just wanted to mention that not all symptoms are reported evenly to AERS. So it partly depends on what we call stimulated reporting, etcetera. And symptoms that are rather common might or might not get reported. I just wanted to mention that.

CHAIRMAN ROSENTHAL: Thank you.

So let's wrap this discussion up, unless there are other comments. So can we go back to the questions at the end of the presentation? I think we've -- I think the committee would like -- Dr. Sachs, you made reference to the fact that there would be another safety review triggered by -- triggered at some point in the future. Is there a sense for when that might be?

The reason I'm asking is, would it be reasonable to link some further discussion of this topic of comorbidities?

DR. MURPHY: We're not getting the time here. I don't think that -- and I'm not sure even if we could if we could tell you, unless we've made it public.

DR. SACHS: Well, the February approval. The February approval for adjunctive treatment will trigger another review.

DR. MURPHY: Okay, so the February approval would theoretically be -- you're talking about a February --

DR. SACHS: February 2011.

DR. MURPHY: So it would be some time next year, the latter part of next year, okay, that we would be coming to this. And I'm not saying definitely that we have it scheduled for the fall meeting or not, because I don't want to make that statement.

CHAIRMAN ROSENTHAL: Fall of 2012?

DR. MURPHY: Yes, yes.

But what we do is we do try to look at common mechanisms of actions or products in the same indication and bring them, if they are fortunate enough to have similar dates. It's like Cary was saying, where we have an action date, because that's the trigger for it.

So we could bring it, either late next year or early in 2013. That would be -- Judith has just sent me a note: "What's the timing on this?" It seems that that would be the timing on it.

CHAIRMAN ROSENTHAL: Okay. That sounds good.

So maybe we can vote on this question now, just with the caveat that at some point towards the end of 2012 or early in 2013 we're also likely to hear a subsequent safety review with additional information pertaining to these questions of comorbidity and co-administration of other medications.

So assuming that that's true, does the committee concur that the FDA should continue with its routine monitoring for safety signal for Intuniv in the interim? All in favor of that?

(A show of hands.)

CHAIRMAN ROSENTHAL: Is there any opposition?

(No response.)

CHAIRMAN ROSENTHAL: I saw no opposition. Dr. Rogol, will you get us started going around the table?

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener, yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Yes, with an additional token of gratitude to the agency and division for considering my comments.

DR. ANDERSON: Garnet Anderson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: Okay, thank you.

We're now half an hour behind on the schedule for a number of reasons. I'll take responsibility as the timekeeper. I think we should take a break, so let's take just a ten-minute break and plan to return at 20 minutes to 11:00, and we'll discuss Lexipro at that time.

(Recess from 10:29 a.m. to 10:39 a.m.)

CHAIRMAN ROSENTHAL: As everyone's finding their seats, Dr. Reed, are you in a position where you can add?

Dr. Reed, in the spirit of having all discussions into the microphone instead of in halls or in other places, Dr. Reed wanted to add something to the discussion that we were just having.

DR. REED: Thank you, Mr. Chairman. I just wanted to make a comment to our colleagues in the office. That is, expanding on what Dr. Rosenthal had brought up on a global basis of looking at other comorbidities and possible drugs, I wanted to follow up briefly on the issue of drug interactions. I agree that in the labeling the drug interactions are appropriately outlined.

But as we move forward in looking at instilling the pediatric footprint into these labels, I don't know the answer to this yet,

and I'm happy to work with you on it, but we might think of using -- adding an additional example or two of more pediatric common drugs that might be related to drug interactions.

For example, we use the classic ketoconazole as a 3A blocker. We appreciate that. I'm not so certain that the practicing pediatrician -- that ketoconazole would come to mind as a common drug for them. We might just think about, are there some other drugs that might be inhibitors or inducers that is more pediatric-friendly, that we might add as an example.

As I said, I was a little reluctant to comment on this because I don't have the answer, but I'm happy to work with you on doing that.

Thank you, Mr. Chairman.

DR. LOUGHRAN: The reason that ketoconazole, of course, is looked at is it's at the far end. It's at the extreme. It tells you sort of what the other limits are. But you're absolutely right that it's the more commonly used drugs that have a lesser effect, but do have an effect, that one would be interested in knowing about. You can't, of course, do drug-drug interaction studies with all of these drugs, but there must be some way of looking at these large databases we now have access to that would help us with that.

Maybe Sentinel would be something we could use to look at that.

CHAIRMAN ROSENTHAL: Thank you for that comment.

Let's move right along to the presentation by Dr. Karesh for Lexipro, the review of adverse events for Lexipro.

I'll just -- Dr. Anderson is recused for this discussion and has stepped away from the table.

All right. So Dr. Karesh 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 the summer of 2008, Dr. Karesh worked as a pediatric hospitalist at Inova Fairfax Hospital, and she has worked as a pediatrician for Kaiser Permanente as well. So a rich clinical experience as well as her experience here.

Thank you.

LEXIPRO (ESCITALOPRAM OXALATE)

STANDARD REVIEW OF ADVERSE EVENTS

DR. KARESH: All right. Today we're going to talk about Lexipro.

(Screen.)

You are familiar with this outline. Please note, we will discuss additional relevant safety labeling for Lexipro after we discuss the pediatric labeling changes.

(Screen.)

Escitalopram, or Lexipro, is an SSRI, originally approved in 2002. The pediatric labeling changes we'll be discussing today occurred in 2009. Lexipro is indicated for acute

and maintenance treatment of major depressive disorder in patients 12 years and older. Lexipro is also approved for the acute treatment of generalized anxiety disorder in adults.

(Screen.)

I am going to outline the regulatory history. Please keep in mind that when exclusivity is awarded it attaches to the moiety, which essentially is the part of the drug that makes the drug work the way it does. Many different drug products may be marketed with the same active moiety.

In July 1998 citalopram, or Selexa, was approved. Citalopram is a racemic mixture that includes escitalopram. In April 1999 a written request for citalopram was issued, and then in April 2002 the citalopram studies were submitted.

July 2002, pediatric exclusivity was awarded for the moiety, citalopram and escitalopram. The escitalopram pediatric studies were submitted May 2008. Then, March 2009, escitalopram was approved for use in pediatric patients with major depressive disorder.

The Lexipro approval was based on a positive pediatric study of each, escitalopram and citalopram.

(Screen.)

This slide lists the placebo-controlled pediatric studies of citalopram of escitalopram. As I just explained, the pediatric escitalopram approval was based on efficacy being demonstrated in each of a citalopram study and an escitalopram

study. The two escitalopram studies alone would not have been sufficient since one of the two did not demonstrate efficacy.

(Screen.)

Here are more details on the two studies used to establish pediatric efficacy of Lexipro for short-term treatment of pediatric patients. You will note that both studies were eight weeks, flexible dose, placebo-controlled studies, with the Children's Depression Rating Scale Revised as the end point. The escitalopram study was in patients 12 to 17 years of age and the citalopram study was in patients 7 to 17 years of age.

(Screen.)

Efficacy of maintenance treatment was extrapolated because we believe the course of the disease and the effects of the drug are sufficiently similar in adult and product patients and we had data from adequate and well-controlled adult studies along with supportive safety data from pediatric studies and comparisons of PK parameters in adult and pediatric patients.

(Screen.)

Now that we've discussed the efficacy results, we'll discuss the safety results. Adverse events were collected in 576 pediatric patients with major depressive disorder, 286 of whom received Lexipro. Overall, the adverse reactions were similar to adults. Common adverse reactions in product patients were back pain, UTI, vomiting, and nasal congestion. 3.5 percent of

pediatric patients discontinued Lexipro due to adverse events, most commonly insomnia.

(Screen.)

Safety and efficacy were not established in pediatric patients less than 12 years of age with major depressive disorder or in pediatric patients with generalized anxiety disorder.

(Screen.)

The pediatric labeling changes that occurred as a result of these studies are listed on this and the following slides. You can see that because Lexipro's indicated for use in product patients, product information is dispersed throughout the labeling in the appropriate sections.

(Screen.)

Now that we've discussed pediatric-specific labeling, for the next four slides we'll discuss safety information on Lexipro labeling, beginning with the boxed warning.

(Screen.)

There is a boxed warning that discusses suicidality in antidepressant drugs as a class and explains that Lexipro is not approved for use in patients less than 12 years of age. Lexipro contraindications are: concomitant use of MAO inhibitors, or pimozide, and hypersensitivity to the ingredients.

(Screen.)

Labeling describes clinical worsening and suicide risk, including that the absolute risk of suicidality is different

across the different indications for antidepressant agents. There was a tendency towards an increase in suicidality in younger patients, and the highest incidence of suicidality was in patients with major depressive disorder.

(Screen.)

There are additional warnings and precautions in labeling, which I've listed on this and the following slides: serotonin syndrome, or NMS-like reactions; discontinuation; seizures, mania, hyponatremia, and abnormal bleeding.

(Screen.)

Impaired judgment and motor skills, caution with concomitant illness, and potential interaction with MAO inhibitors.

(Screen.)

Now that we've discussed the studies and labeling, we'll turn our attention to escitalopram use. In the outpatient setting, approximately 127 million prescriptions were dispensed between October 2005 and September 2010. The projected number of prescriptions decreased between those four years.

(Screen.)

Pediatric patients accounted for approximately 4 percent of the patients receiving escitalopram prescriptions, with the majority of the pediatric patients being adolescents.

(Screen.)

The most common prescribing specialties for escitalopram

were general practice, family medicine, and doctor of osteopathy.

Pediatric practitioners accounted for approximately 1.3 percent.

(Screen.)

The most common diagnosis codes for different age groups are listed here.

(Screen.)

Now that we've established the foundation of escitalopram use, we'll discuss the adverse events reports. There were 352 pediatric crude count reports since Lexipro was initially approved. Please note that there were 36 crude count pediatric deaths.

(Screen.)

Although we start with 36 crude count pediatric fatal reports, I am going to walk you through how we wound up with 31 pediatric fatal cases since initial approval. Of the 36 pediatric fatal crude count reports, 5 were duplicates, 1 was an adult, and 1 was miscoded as nonfatal but was actually a fatality, which adds up to 31 pediatric fatal cases since initial approval.

Please remember that there are 31 pediatric fatal cases.

But before we discuss those cases, I'd like to discuss the number of pediatric fatal adverse event reports specifically since pediatric approval.

(Screen.)

Since Lexipro was approved for use in pediatrics, there were 78 crude count pediatric reports, including two fatalities.

Additionally, there were 30 deaths of unknown age. FDA looked at these 30 reports to assess whether the ages of these patients could be determined.

(Screen.)

As before, I'm going to walk you through how we narrowed down our crude count. In this case, of the 34 crude count reports where the age was unknown since pediatric approval, 6 were duplicates, 8 turned out to be adult cases, and for 13 of them age could not be determined, which leaves 3 additional pediatric fatal case reports to add to the 31 pediatric fatal case reports determined earlier that I asked you to make a note of. Therefore, there are 34 total pediatric fatal cases that we'll be discussing today.

(Screen.)

Of the 34 fatal pediatric reports, 12 were in utero exposure to escitalopram, 21 were reports of patients who completed suicide, and 1 was a patient who drowned following a seizure. Please note, there is limited information for all these AERS cases.

(Screen.)

The age and death of patients with in utero exposure to escitalopram is presented on this slide. Of the 12 fatal in utero exposure reports, the dose was reported for 5 cases. The range was 10 to 20 milligrams and the median was 10 milligrams. Congenital anomaly was reported for 9 of the 12 cases.

Lexipro is labeled as pregnancy category C and labeling states: "There are no adequate and well-controlled studies in pregnant women. Therefore, escitalopram should be used during pregnancy if the potential benefit justifies the potential risk to the fetus."

(Screen.)

As I explained earlier, there were 34 pediatric fatal adverse events reports, and of those 34 21 were completed suicides. The age of those patients when they died is presented on this slide. As we discussed, Lexipro contains a boxed warning regarding suicidality in antidepressant drugs as a class.

(Screen.)

The method of suicide and the gender for the completed suicide reports is presented on this slide.

(Screen.)

This slide lists the reasons the patients who committed suicide were treated with Lexipro. Additionally, the time between starting escitalopram and completing suicide was reported for 17 of the 21 cases, with the range being 11 days to 2.4 years and the median 46 days.

(Screen.)

The daily dose of escitalopram was reported for 14 of the 21 cases, with a range of 5 milligrams to 20 milligrams. Concomitant medications were reported for 10 of the 21 cases, and of these none are labeled for increasing suicidality. Past

medical history was provided for seven cases and included suicidal ideations, behavior, or threats for five of the reports, possible history of suicide attempts for one, and self-injurious behavior for one.

(Screen.)

As I mentioned earlier, there was one report of a patient who drowned following a seizure. Seizures are a labeled adverse events.

(Screen.)

I've already shown you this table of crude count adverse event reports since pediatric approval, but this time, instead of focusing on the fatal reports, I'd like you to please note the 71 non-fatal serious pediatric events, adverse events reports.

(Screen.)

I'm going to walk you through how we wound up with the 56 non-fatal serious pediatric adverse event reports. Of the 71 pediatric non-fatal crude count reports, 14 were duplicates and one was actually a fatality that was included in our earlier discussion of fatal pediatric reports, which leaves us with 56 non-fatal serious pediatric adverse event reports, which we will now discuss.

(Screen.)

Of the 56 non-fatal serious pediatric reports, 32 were in utero or trans-mammary exposure reports. The breakdown of the others, which we will discuss in more detail, is listed on this

slide.

(Screen.)

Of the 13 psychiatric events, 5 involve suicide attempts, 2 suicidal ideation, 1 self-injurious behavior, 2 hypomania, 2 hallucinations, and 1 agitation. All of these are labeled adverse events.

(Screen.)

The two hypomania cases are described on this slide. Please note, escitalopram labeling includes hypomania.

(Screen.)

The two hallucination reports are described here. The first patient was reportedly tested for cytochrome P450 gene and was determined to be a poor metabolizer. Labeling states that your metabolizer status might influence your exposures. Escitalopram, Carbamazepine, and the lamotrigine labeling all include hallucinations.

(Screen.)

The case report of agitation is described on this slide. Escitalopram labeling includes agitation.

(Screen.)

The first of the two gastrointestinal adverse event reports is presented on this slide. Although Lexipro is not labeled for oropharyngeal spasms, the patient was on aripiprazole, which may explain the adverse event.

(Screen.)

The second gastrointestinal report was a 16 year old male on Ibuprofen. Escitalopram labeling does contain a caution regarding the concomitant use of NSAIDs.

(Screen.)

The first of two cardiovascular adverse event reports is on this slide. A 15 year old male experienced syncope, which is a labeled adverse event for both escitalopram and levalbuterol, a concomitant medication for this patient.

(Screen.)

The second cardiovascular adverse event report involved a 10 year old male who was diagnosed with lithium toxicity. Lithium toxicity is described in the lithium labeling. The Lexipro labeling states that: "Coadministration of citalopram and lithium had no significant effect on the pharmacokinetics of citalopram or lithium. However, lithium may enhance the serotonergic effects of escitalopram. Therefore, caution should be exercised when Lexipro and lithium are coadministered and plasma lithium levels should be monitored."

(Screen.)

The first of two nervous system adverse event reports is described on this slide. A 12 year old male experienced abnormal posturing. Escitalopram labeling includes dyskinesia and extra pyramidal disorders. Additionally, alprazolam, a concomitant medication, labeling includes abnormal involuntary movement.

(Screen.)

The second nervous system adverse event report included a -- involved a 16 year old male who experienced loss of consciousness, convulsion, and hyperventilation during a 10-minute period of time. Escitalopram labeling includes convulsions, nightmares, and hallucinations and sertraline labeling includes convulsions, hallucinations, and hyperventilation.

(Screen.)

There were five miscellaneous adverse event reports: recurrent leukemia, fatigue, thick tongue, diabetes with decreased weight and abdominal pain, and anxiety, drug ineffective, eating disorder, and fatigue. Escitalopram labeling does include fatigue, diabetes, decreased weight, abdominal pain, and anxiety.

(Screen.)

In summary, escitalopram labeling includes a class boxed warning regarding suicidality and antidepressant use in pediatric patients. The boxed warning also states that Lexipro is not approved in pediatric patients less than 12 years of age. Lexipro labeling includes information from the pediatric clinical trials. The pediatric-focused safety review did not identify any new pediatric safety concerns, so FDA plans to continue routine monitoring of adverse events in pediatric patients. Does the Pediatric Advisory Committee concur?

I would like to acknowledge the people listed on this slide.

CHAIRMAN ROSENTHAL: Thank you for your presentation.

Are there questions or comments regarding Lexipro? Dr. Towbin?

DR. TOWBIN: Well, I have a few comments. One is, as I review the treatment trials it looked as if if one broke out the African-American community that there was a lack of efficacy in that population for the trials that were submitted. I was just wondering how that gets handled in the labeling and information available to people, if there might be a suggestion that in the trials that were submitted this would be a population less likely to respond.

DR. LOUGHRAN: We always look at various subgroups based on age, race, gender, and sometimes other factors, and you always find -- I forget exactly what the proportion was of the ethnic minorities in this particular study, but they're generally small. I think it's very difficult to interpret findings based on these multiple subgroup analyses.

So we generally -- we generally don't highlight that in the labeling, and we don't honestly know how to interpret it. I mean, I think if you wanted to -- and it's probably unlikely that that particular subgroups is unresponsive. But it's an open question until you specifically do that study.

But it's always a challenging issue looking at various subgroups, and of course you can't study every subgroup prior to approving a drug. But it's an ongoing challenge.

DR. TOWBIN: I think that's a fair response. I think

that the concern I have is that, although one would expect there should not be a specific kind of effect of race in response to this agent, there isn't evidence that it was as effective. I do agree that for these studies recruitment -- I don't know the exact proportion off the top of my head, but I do agree that the recruitment was less than what one might see in the general population. But I would have been happier if this signal, when you broke that out, was at least suggestive of a stronger response, and I don't think that was there.

CHAIRMAN ROSENTHAL: Yes, Dr. Wagener?

DR. WAGENER: I guess I would ask the question, should there be a black box warning about pregnancy exposure, when you look at the number of fatalities there were in infants? This is a drug that there has been other evidence of its prenatal exposure leading to things like pulmonary hypertension. I know that's in the labeling, but that's a pretty high number of fatalities that may have been avoided.

DR. KARESH: I defer to the division. Since I do pregnancy, I could speculate, but I'd rather defer to the division.

DR. LOUGHRAN: Again, I think you have to keep in mind that these reports are coming out of a very large exposed population. There have been a number of registry studies done with SSRIs and in general you don't find a signal coming out of those, except for -- the one exception is paroxetine. We have

seen a signal there, and actually paroxetine has a category D for pregnancy. The rest have a C, and that's based on animal findings, not on human findings.

So I'm a little bit reluctant to make too much of this relatively small number of cases taken out of -- the denominator here is really quite enormous. So I think -- again, I think it's a problem of interpretation and making too much of these few cases that turn up in AERS.

CHAIRMAN ROSENTHAL: May I just add that it seemed to me -- and I don't have the table in front of me, but it seemed to me that when one looked through the types of neonatal and infant problems that these babies who had been exposed in utero were having that it didn't seem like there was a consistent theme around potential teratogenic mechanisms or the like.

DR. LOUGHRAN: And the times when they occurred were quite broad in terms -- some early, some as late as I think a year later. Very difficult to know what to do with that.

CHAIRMAN ROSENTHAL: Dr. Towbin?

DR. TOWBIN: Another thing I wanted to address is, these studies began adolescents on 10 milligrams of escitalopram, and it's been observed in the pediatric population that the risks for activation kinds of reactions are greater in this developmentally younger group. I was just wondering if there was information that was available or if people had given consideration to suggesting that the recommended starting dose be something more like 5

milligrams, which is a dose form that's available of this agent.

The studies weren't done and so it's a question that I think may not be possible for the division to answer. But I am concerned that the frequency of these kind of activation reactions sometimes attributed to hypomania may actually be a result of initiating a dose that's excessive.

DR. LOUGHRAN: It's a fair question, but we don't have data. These studies unfortunately were flexible dose studies rather than fixed dose studies and they did start at 10. So it's a reasonable question. We just don't have any basis for putting that recommendation in the label.

CHAIRMAN ROSENTHAL: Are there other questions or comments about Lexipro?

(No response.)

CHAIRMAN ROSENTHAL: No. Okay, all in favor of continuing the standard safety assessments and surveillance for this medication, please raise your hands? (A show of hands.)

CHAIRMAN ROSENTHAL: Is anyone opposed?

(No response.)

CHAIRMAN ROSENTHAL: All right, let's go around the table. Dr. Rogol?

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener, yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: All right, thank you very much. We can now invite Dr. Anderson back to the table.

For this discussion of Valcyte, Dr. Romero is recused. Dr. Karesh will also be presenting the Valcyte review of adverse events.

You can proceed.

VALCYTE (VALGANCICLOVIR HYDROCHLORIDE)

STANDARD REVIEW OF ADVERSE EVENTS

(Screen.)

DR. KARESH: Here is the outline that you're now familiar with.

(Screen.)

Valganciclovir is a CMV antiviral agent. Tablets were approved March 2001 and the Valcyte for oral solution was approved August 2009. The BPCA PREA labeling changes that we're going to discuss today were incorporated August 2009.

(Screen.)

Valcyte is approved in pediatrics for the prevention of CMV disease in high-risk kidney or heart transplant patients 4 months to 16 years of age. In adults it is approved to treat CMV retinitis in patients with AIDS and to prevent CMV disease in high-risk kidney, heart, or kidney-pancreas transplant patients.

(Screen.)

You can see the limitations of use on this slide. Valcyte is not indicated for use in liver transplant patients. Additionally, safety and efficacy have not been established to prevent CMV disease in solid organ transplants other than those we discussed, to prevent CMV disease in pediatric patients less than 4 months of age, or to treat congenital CMV disease.

(Screen.)

Valganciclovir is an ester of ganciclovir and exists as tablets and oral solution.

(Screen.)

Dosing for pediatric patients is based on body surface area and creatinine clearance.

(Screen.)

When you hear about the adverse events, I would like you to keep additional labeling in mind. There is a boxed warning regarding hematologic toxicity, carcinogenicity, teratogenicity, and impairment of fertility.

There are important warnings and precautions, including

hematologic effects, impaired fertility, teratogenicity, mutagenicity, carcinogenicity, and renal failure.

(Screen.)

Now that we've discussed the background information, we'll turn our attention to the four pediatric studies. Studies 1 and 2 were PK studies in two different populations, renal and liver transplant recipients, and these studies helped select the appropriate dosage for the third study, which was an open-label, noncomparative exposure response study in pediatric solid organ transplant recipients. The fourth study was an open-label exploratory study in neonates to evaluate the treatment of congenital CMV disease.

Ultimately, efficacy in pediatric patients was extrapolated from adult studies. The course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients.

(Screen.)

Overall, Valcyte for oral solution and tablets were studied in 109 pediatric solid organ transplant recipients. Additionally, 24 neonates with symptomatic congenital CMV disease were studied.

(Screen.)

Now that we've discussed the population studied, we'll discuss the PK, safety and efficacy results. As I explained, based on the results from studies 1 and 2, the PK studies in renal

and liver transplant recipients, a dose was selected for study 3.

Dose PK results revealed similar ganciclovir exposures across organ types and age ranges and that the ganciclovir exposures were comparable to those from adult patients receiving Valcyte 900 milligrams daily.

(Screen.)

The safety results were similar in pediatrics to adults. Furthermore, no CMV disease was reported, although CMV viremia without additional symptoms was reported in 11 percent of the patients.

(Screen.)

The most common reported adverse events and lab abnormalities are listed on this slide.

(Screen.)

As explained earlier, efficacy for CMV prevention in solid organ transplant recipients was extrapolated. The extrapolation of efficacy was based on data from a pediatric open-label trial and demonstration of efficacy in adult patients.

(Screen.)

Since use was approved in pediatrics, information gained from the pediatric studies were dispersed throughout labeling in the appropriate sections, as listed on this slide.

(Screen.)

Now we are going to switch gears and discuss Valcyte use. As you can see, the total number of prescriptions dispensed

has increased from approximately 8800 in 2001 to approximately 104,000 in 2009. There was a cumulative total of approximately 692,000 dispensed prescriptions between January 2001 and August 2010. The number of dispensed prescriptions for all of 2010 was not available when the data was extracted.

(Screen.)

You can see from the use data on this side that pediatric use is 4.7 percent. Data from 2001 was not available.

(Screen.)

The most common prescribing speciality for Valcyte was nephrology, followed by unspecified. Pediatric providers was 5 percent. The top diagnosis code for adults was heart transplant status.

(Screen.)

Now that we've set the framework by discussing the Valcyte studies, labeling changes, and use, we'll now discuss the adverse event reports. As shown on this slide, there were 20 pediatric crude count reports.

(Screen.)

Of the 20 pediatric adverse event crude count reports since approval, four were duplicates, one miscoded, and one transplacental exposure. Of the remaining 14 adverse event reports, all were serious, including 3 fatalities.

(Screen.)

Here is a listing of the 14 serious adverse events. As

we discuss the reports, please keep in mind in most instances the adverse events appear related to concomitant medications and-or the patient's underlying disease.

(Screen.)

Of the 14 pediatric serious adverse events, the reason for use is listed on this slide. As you recall, in the U.S. Valcyte is approved to prevent CMV disease in high-risk kidney or heart transplant patients 4 months to 16 years of age.

(Screen.)

Now we're going to discuss the three fatal pediatric cases. The first involved a 13 year old male with ALL, status post-stem cell transplant, who received valganciclovir for CMV retinitis for approximately 2 months and acyclovir for suspected herpes encephalitis. His leukemia relapsed and he developed fatal renal failure.

As I explained earlier, Valcyte is approved to treat CMV retinitis in adults with AIDS.

(Screen.)

The second fatal case involves an 11 year old male who was on valganciclovir for approximately 3 months for CMV prophylaxis status post-kidney transplant. He developed H1N1 flu and died secondary to pneumonitis. Valcyte is approved to prevent CMV disease in pediatric patients status post-kidney transplant.

(Screen.)

The third fatal pediatric case involved a 4-month-old female, status post-stem cell transplant, who received either valganciclovir or ganciclovir for the treatment of CMV. 60 days post-transplant, she had an increased CMV viral load and received valganciclovir and foscarnet. She ultimately developed persistent hypoxia pneumonitis, required mechanical ventilation, and died secondary to reported delayed pulmonary toxicity syndrome and CMV resistance.

Valcyte is not approved to treat CMV after stem cell transplant.

(Screen.)

Now that we've discussed the three fatal pediatric cases, we'll turn our attention to the 11 non-fatal serious pediatric cases, and I'll discuss them by organ system, beginning with the three hematologic serious non-fatal case reports.

(Screen.)

The first of the three hematologic case reports involved a 16 year old female, status post-lung transplant, on multiple medications, who received Valcyte for CMV prophylaxis. She developed leukopenia, anemia, and thrombocytopenia.

(Screen.)

The second of the three hematologic cases involved a 5 year old male, born at 35 weeks gestation, who required a kidney transplant. He received Valcyte to treat a reactivated CMV infection and developed blood and electrolyte abnormalities with

secondary seizures.

(Screen.)

The third hematologic case involved a 7 month old female who developed hemolytic anemia. Although the underlying indication was not reported, CMV infection itself may be associated with hemolytic anemia.

(Screen.)

Of the 11 pediatric serious non-fatal adverse events, 2 were pathogen-resistant case reports, as described on this slide.

(Screen.)

Valganciclovir labeling does discuss viral resistance.

(Screen.)

The two CNS case reports are described here. Please note, both patients were on cyclosporin and the cyclosporin labeling does describe the adverse events these patients experienced.

(Screen.)

There were two post-transplant lymphoproliferative disease cases.

(Screen.)

There was one report of a 7 year old female who experienced increased hepatic enzymes and hepatic steatosis.

(Screen.)

There was one case report of a patient with decreased appetite and an ankle fracture.

(Screen.)

So in summary, information from pediatric studies is incorporated into labeling. No new safety signal was identified from the adverse event reports and FDA plans to return to routine monitoring. Does the Pediatric Advisory Committee concur?

(Screen.)

I would like to acknowledge the folks listed on this slide.

CHAIRMAN ROSENTHAL: Thank you.

Discussions about Valcyte?

(No response.)

CHAIRMAN ROSENTHAL: No discussion. All right. Does the committee concur that we should -- are there any specific questions or ticklers that the agency would like the committee to reflect on that aren't reflected in the slide?

DR. MURPHY: I don't think so. I want to introduce our member from the division, but this product's being used in persons who are obviously very sick and complicated, and you saw from the presentations that we don't think we saw anything that could be described as either new or directly attributable.

So I'd like to have our division representative introduce himself and then see if he has any comments?

CHAIRMAN ROSENTHAL: Yes, please.

VOICE: Thank you. I don't have any specific comments. It's the only drug we have available. Even though it is used

off-label, we use it on label for the bone marrow transplant, and we know that it has a great spectrum of adverse events, but it's our only option that we have at this time. And most of the adverse events could be easily monitored, like the hematological.

CHAIRMAN ROSENTHAL: Thank you. Do you mind introducing yourself?

VOICE: My name is (inaudible). I'm a medical officer with the Division of the Antiviral Drugs Products.

CHAIRMAN ROSENTHAL: Thank you, and thank you for joining us and for your comment.

Comments from the committee?

(No response.)

(No response.)

CHAIRMAN ROSENTHAL: All right. All in favor of returning Valcyte to routine monitoring?

(A show of hands.)

CHAIRMAN ROSENTHAL: Does anyone oppose that?

(No response.)

CHAIRMAN ROSENTHAL: Okay, let's go around the table. Dr. Rogol?

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Concur.

DR. ANDERSON: Garnet Anderson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder. Yes.

DR. BHATIA: Jatinder Bhatia. Yes.

CHAIRMAN ROSENTHAL: Okay. Thank you very much.

Before we go on to the next step in our somewhat fluid agenda, Dr. Towbin wanted to make a comment, one last comment about Lexipro, and I just want to give him a moment to make his comment.

DR. TOWBIN: I just wanted to say that the comments that we made related to Intuniv, the extended release form of guanfacine, those concerns about polypharmacy and populations also apply to escitalopram. So my hope was or is that as we think about the review for guanfacine that some of those same methodologies might be applied in the escitalopram or Lexipro prospective use reviews.

CHAIRMAN ROSENTHAL: Thank you very much.

So at this point in the agenda we're going to move things around a little bit. For those of you who have arrived late, there was -- we've been experiencing quite a scheduling challenge today because a number of people are hung up in various airports because of weather and other matters such as that.

So the next presentation will be Dr. Skip Nelson's review of the matters taken up by the Ethics Subcommittee of the Pediatric Advisory Committee just last week. So thank you for joining us, Dr. Nelson.

DISCUSSION REGARDING OUTCOMES FROM THE
ETHICS SUBCOMMITTEE MEETING ON MAY 11, 2011

DR. NELSON: Thank you. In the interest of time and to allow for some discussion on the part of the three members of the committee that attended our session last week, I'd like to just make some general comments about the topic. Alex, Geof, and Ken were both there and so I'd welcome their additions.

Let me just first by way of introduction to those people that are new to the committee, you may not be aware that there is a Pediatric Ethics Subcommittee of this committee. It's the only committee to my knowledge within FDA that has such a subcommittee, and this committee -- this subcommittee as well as this committee is also chartered to be able to offer advice on the ethical issues in in the conduct of pediatric clinical investigations.

As part of that, we do occasionally convene the Pediatric Ethics Subcommittee to offer such advice. At times there might be recommendations that would come through this committee then to the Commissioner or to the Secretary. But in this case the meeting we held last week was a general discussion of issues that would inform our writing of guidance and not any particular set of recommendations that came forth.

So what I'll just be providing is a general outline of that discussion. But I will say as an introduction, it's kind of hard to summarize in a few minutes six hours of conversation. So I don't want you to take away that what I happen to mention is the only thing that was discussed. It might not even be the most important thing that was discussed, and we'll be going back through the transcripts and mining it, if you will, for much more information as we reflect on this.

So the topic that we discussed was the issue of exploratory IND clinical studies. For those of you who may not be familiar with that, a term often that's called phase zero trials in the literature. In January of 2006, FDA issued a guidance on the conduct of exploratory IND studies, which was with the intent, given that these studies involved sub-therapeutic doses of medications and therefore lower drug exposure, the guidance primarily goes through a how sponsor may conduct those kinds of trials without necessarily doing all of the pre-clinical toxicology studies that are done when one is going into a classic phase 1 trial, where you're driving that dose either to maximum tolerated dose or to some therapeutics effect.

In that guidance, it specifically indicates that pediatrics is often not used. In fact, there's an exclusion in that, and so the question that we had was how one might approach these kinds of trials, where you have a sub-therapeutic dose, which by definition doesn't offer any prospect of direct benefit

in a pediatric population, and looking at that issue through the lens of the additional protections for children that's included in Subpart D of our regulations, 21 CFR 50 Subpart D.

Without belaboring the regulatory language, the basic question is, absent any prospect of direct benefit to that child, the risk must be low, and how can you consider the risk low for certain populations? The language we use in our regulations is "a minor increase over minimum risk or a minimal risk."

So that was basically the question that the committee was asked to think about, is under what circumstances could one consider such an exploratory IND trial appropriate within the additional protections for children in research. We discussed that both for drugs that would potentially be greater than minimal risk and for drugs that could be considered a minor increase over minimum risk, and if you then gave less of it, under what circumstances might you consider that risk reduced.

It was a rich discussion with a lot of considerations given on those, so I'm not going to try and summarize that. The one point that I did take away is that at least the intent of the guidance, which is to lower the bar for pre-clinical toxicology studies for adults, I did not get a sense from the committee that they thought that the data that one would need to be able to assess this lower risk exposure could necessarily forego those kinds of studies in pediatrics.

So I don't think, from a general guidance approach, that

it was clear that one could take that IND guidance and apply it to pediatrics in a simple fashion. It was a much more complex discussion.

So we had -- beyond the discussion of those two questions, we also discussed other general ethical issues that need to go into the assessment of these trials, and we also discussed how one could be assured of adequate protections for children in research. Towards the end of our conversation, given the known variability within the IRB system, it was another topic that we discussed.

But rather than sort of my going through that, what I'd like to do is just stop there and allow Alex, Jeff, and Ken to add their observations to the meeting, and then see if there's any questions or comments about what I've said.

CHAIRMAN ROSENTHAL: Dr. Rakowsky?

DR. RAKOWSKY: Thank you, Skip, for a nice summary.

I think it's interesting that a lot of times on this committee we do propose studies, and this was a very vivid reminder that there are only certain mechanisms under which an IRB can approve a pediatric study. So I think a lot of the discussion spun around the fact that if you look in the regulations, and you mentioned 21 CFR Part 50 Subpart D, what I think is important for all of us to always keep in mind when we talk about proposals, there is really no mechanism for an above minimal risk study in a healthy child, because at risk level 3 or the 53 studies you

almost have to have a child with a condition.

So I think it was a really good discussion about in the exploratory IND field, how do you actually kind of peg them or place them within the regulatory framework that the IRBs have to work under, to somehow get the studies potentially approved or looked at.

It was a nice sort of juxtaposition of the regulations and the sort of ethics of these studies.

CHAIRMAN ROSENTHAL: Dr. Towbin?

DR. TOWBIN: Well, for the agency to have devoted the resources to this question I think is admirable, and I appreciated the expertise of the group that was gathered. I think the summary that you offered, Skip, was an excellent one.

The thing that I carried away from this was how there could be circumstances under which these things could be feasible, but the standard that would need to be set would be that there literally would be no other alternative, that there may be a value in thinking about these kinds of studies and they actually do contribute to knowledge, but there may be in fact other ways to get this information, and that part of the skill is thinking about applying these kinds of methods in a population where the ethical burden is really protected to the greatest degree.

CHAIRMAN ROSENTHAL: The only thing that I would add is really just an affirmation of what Dr. Towbin said. I think it's very important to the protection of this vulnerable population

that the agency continue to invest resources when needed to clarify these important points, as has been done with each of the Pediatric Ethics Committee meetings in which I've been lucky enough to participate.

I think that, Dr. Nelson, I'll just tell you that I think you do a great job both assembling people and framing these very difficult ethical questions in ways that the panels can dissect the issues involved and arrive with -- come to some place of insight that allows for guidance for industry and others in considering ways to more safely and effectively study things in children.

So once again I think you've done a great job, and I think that the topics discussed in this particular meeting were -- there was a change in the meeting because the sponsor changed the architecture of a study that had been proposed and that sort of changed the flavor of the meeting. But in the end I think the discussion will provide grist for the guidance mill that I know that you're working on. So we look forward to seeing what comes from that, and again I appreciate your efforts in helping to clarify these tough ethical questions in pediatric research.

Dr. Goldstein, you had a question?

DR. GOLDSTEIN: Yes. Skip, I'm sorry I couldn't come to the meeting. But I was wondering, given the -- given the clear prescribed pathways for pre-clinical evaluations of new drugs in other areas, carcinogenicity, etcetera, oftentimes when it comes

to pediatric studies pediatric or juvenile models are not used and you go straight to -- industry often goes straight to clinical trials.

There may be good reason for that, because usually there aren't particularly good juvenile models of a particular disease.

But nonetheless there are juvenile models at least of healthy individuals and you could do that in more than one species.

Was there discussion about using juvenile models in more than one species and using the paradigm of other pre-clinical development hurdles that need to be overcome in this instance? I think at the very least, that would give some additional information and some comfort in terms of pharmacokinetics and safety in this area.

DR. NELSON: There was -- I guess in fairness, a couple of comments. The sort of hypothetical protocol that served as the point of discussion was the use of pharmacological drug probes for looking at cytochrome P450 metabolism and using sub-therapeutic doses in that context.

So in fairness, the protocol didn't lend itself to the kind of question that you're asking, because the products that are often used for this, though not approved necessarily for this use, are already marketed or, for example, caffeine, which you may have had some today as well. So that wasn't discussed.

What was discussed was the exploratory IND suggests a lower bar for doing pre-clinical toxicology and I think the

general sentiment was that it wouldn't be appropriate to lower the bar in pediatrics. What we didn't discuss was whether the bar should be higher. We didn't get into the specific issues of what pre-clinical toxicology studies or pre-clinical modeling studies are routinely done in pediatric drug development. So that was not a topic that we got into.

CHAIRMAN ROSENTHAL: Dr. Murphy?

DR. MURPHY: Geof, I just wanted to put on the table that the committee, because we are having quite a change in membership and a lot of new members, and we are doing some training to prepare you for the next couple days, but we obviously have a lot of background training that we need to do.

I think if you have particular areas of interest or concerns or questions about how do we do regular product development, how do we address some of these ethical issues, when would it that you guys would be involved in these ethical discussions? If you have questions, I'm volunteering you, Geof, to receive those questions and let us know, because we all are in the process -- you'll hear some more from Ann Meyers as the days go on, but in the process of redoing our training.

So questions that you would like to have addressed during that training would be of interest to us, because some of you may be sitting here going, why is Dr. Nelson talking to us about these ethical trials? It's because the conduct of the trials in children are obviously driven by different underpinnings

from an ethical perspective, and this committee will be taking recommendations from the subcommittee and you will be asked to be on the subcommittee.

So we just added to your list of responsibilities, in case you didn't know that and nobody mentioned it to you.

So Dr. Nelson is someone that you may be hearing from, even when we don't have a full committee meeting.

So thank you.

CHAIRMAN ROSENTHAL: Dr. Nelson, would you like to speak to the other contexts in which the Pediatric Advisory Committee has worked in the past?

DR. NELSON: Well, I think there's two general areas. In the area of what I would call general advice, we had a meeting that now is maybe a little less than two years ago, where we looked specifically at the topic of the prospect of direct benefit and how that's understood in specific clinical trials, using three different hypothetical cases.

One case was an HIV vaccine. Another was stem cell, and I'm now blocking on the third. Oh, it was a growth study in an inhaled steroid, and how do we understand the prospect of direct benefit and analyze those trials from an ethical perspective within the context of the protections in Subpart D. So that was very useful.

This most recent meeting I think was useful because, if you look in the literature, there's no discussion pretty much of

exploratory IND trials in pediatrics. It's a little bit of a sort of leaning-forward topic. In adults it's often talked about in terms of oncology and drug targeting, but in fact there are no pediatric examples even hypothetical that exist on that. That's why it was pretty much limited to drug metabolism.

The other area that the committee is involved in is if there happens to be a referral for review under a category called 50.54, which is basically where a local IRB decides that a trial is both ethically sound and scientifically necessary, but yet can't be approved by the local IRB under one of the three conditions that exist: either minimal risk; greater than minimal risk, prospect of direct benefit; or no prospect of direct benefit, minor increase over minimal risk.

If they feel that they can't approve it under those three categories, but yet it ought to go forward, they can refer it, and then the committee would meet. Under that circumstance, there would then be a formal report to this committee and then a review of those recommendations that would then move forward to the Commissioner and the Secretary if it's HHS-funded for a determination about whether that trial should go forward.

So that's the other context that that committee can meet in.

CHAIRMAN ROSENTHAL: Thank you.

DR. NELSON: I will say, we can't meet without at least two members of this committee on it. More are certainly welcome,

but I usually invite three, as you saw from your travel plans today. I always invite three in case one doesn't make it.

CHAIRMAN ROSENTHAL: I would just like to say, from my personal experience attending a few of these meetings, for those members on the committee, if the opportunity arises I would strongly encourage you to participate. The work of the Ethics Committee is different. It will use a different hemisphere of your brain than what's used in this committee, and both Dr. Nelson and Dr. Roth-Klein do an excellent job, and they also do an excellent job bringing together some of the great minds in ethics.

Yes, Dr. Reed?

DR. REED: I too would like to applaud the efforts and apologize that I couldn't make it. But in that regard, once the minutes or the discussion is transcribed will that be automatically sent out to committee members, or how can we see, learn from the day when we weren't there?

DR. NELSON: Two things. First of all, we'll produce what's called flash minutes, which is basically a brief summary. But again, I think that'll be a bit schematic. The transcription is obviously made public and we'll be going through that in more detail. Then again, this will be incorporated into guidance. I can't tell you when that will be available for review, but certainly my hope is at least some of the topics may then be reviewed in association with the meeting that you may have in the spring of 2012. So my hope that we could then convene a

discussion of some of these topics at that time.

DR. REED: Thank you.

CHAIRMAN ROSENTHAL: Thank you very much, Dr. Nelson.

Let's move along with the agenda if there are no other questions on the topic of the Ethics Committee. Now, we were going to revisit issues raised in a prior Pediatric Advisory Committee on the topical calcineurin inhibitors, both Elidel and Protopic. I understand that representatives from Novartis and from Astellas are here and are ready to provide us with short presentations on their material.

Just while we're getting set up here, when you come to the mike please first introduce yourself so we all know who's addressing us. Then for these presentations, if you can please try and keep them under -- or to ten minutes or not much more.

TOPICAL CALCINEURIN INHIBITORS

INTRODUCTION BY PAUL AFTRING, M.D.

DR. AFTRING: Good morning. Thank you, Mr. Chairman, members of the committee. My name is Paul Aftring. I'm Global Program Medical Director for Novartis Pharmaceuticals. I am here today to present an update on Elidel on behalf of Valeant International-Barbados. Novartis has recently closed a global divestiture with Mehta. Mehta has subsequently appointed Valeant as the distributor of Elidel in the United States. The NDA for Elidel was transferred to Valeant last week, May 11th.

We want to thank the FDA for the opportunity to address

the committee today.

(Screen.)

This is just a brief overview of what I'll discuss today: the current U.S. indication for Elidel, some information on prescription usage between 2005 and 2010, brief comments on the medical need, review of several pieces of data relevant to the safety profile of Elidel, and some conclusions on behalf of Valeant and Novartis.

(Screen.)

So just to remind you, in 2005 potential questions or potential concerns regarding the long-term safety of topical calcineurin inhibitors were brought forward, specifically a possible association with malignancy. In early 2006 Novartis and the FDA agreed on label changes for Elidel.

(Screen.)

This represents the current U.S. indication. Elidel cream is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immune compromised adults and children two years of age and older who have failed to respond adequately to other topical prescription treatments or when those treatments are not advisable. Elidel cream is not indicated for use in children less than two years of age.

Also at that time, a boxed warning was added to the U.S. prescribing information. The boxed warning reads: "Long-term

safety of topical calcineurin inhibitors has not been established.

Although a causal relationship has not been established, rare cases of malignancy, for example skin and lymphoma, have been reported in patients treated with topical calcineurin inhibitors, including Elidel cream. Therefore continuous long-term use of topical calcineurin inhibitors, including Elidel cream, in any age group should be avoided, and application to areas of involvement with atopic" -- "application limited to areas of involvement with atopic dermatitis." Again, Elidel cream is not indicated for use in children less than two years of age.

(Screen.)

Following these concerns being raised, a medication guide was also implemented. This represents the prescription usage for Elidel beginning in 2005 and proceeding through to 2010.

As you can see, there has been a dramatic and continuous decline during this time frame. The overall prescriptions have been decreased by about 82 percent. The prescriptions in the population less than two years of age, the population that is not indicated for Elidel use, have decreased by 98 percent during this time period.

(Screen.)

Elidel continues to fulfil a medical need that's important in the treatment of atopic dermatitis patients for whom it is indicated. Atopic dermatitis is a condition associated with symptoms that can result in skin damage, secondary infection,

sleep loss, and have a significant impact on quality of life. Indeed, in a survey conducted of patients and their caregivers with atopic dermatitis some 75 percent maintained that effective treatment of atopic dermatitis would be the single most improvement, single greatest item that could improve their quality of life.

(Screen.)

Elidel cream is an important therapeutics alternative to topical corticosteroids for mild to moderate atopic dermatitis. In a clinical program for Elidel cream, randomized controlled trials have demonstrated that the product effectively controls eczema and pruritis in children with facial dermatitis intolerant to topical corticosteroids. Indeed, the upper panel shown on this slide represents the clearing -- the complete clearing or near clearing of facial atopic dermatitis in children ages 2 to 11 years old. As you can see, Elidel cream provides a significantly greater effect than the vehicle, with an early onset and continued improvement during the course of the study.

(Screen.)

Also, head and neck dermatitis in adolescents and adults who are intolerant to topical corticosteroids, Elidel again has a significantly effect. The lower panel represents a study conducted in children 12 years and older -- or children and adults above 12 years of age. As you can see, in this case the EZ score for head and neck dermatitis is significantly affected by Elidel,

with greater improvement at the earliest time right through the course of the study.

It has also been noted that Elidel treatment is associated with improvement of skin atrophy during corticosteroid-free periods.

(Screen.)

What is shown here is a summary of a series of epidemiologic studies that were specifically designed to address the question of the association of topical calcineurin inhibitors with malignancies. This series of studies is also part of the FDA review that you have received. All of these studies conclude that there is no increased risk of malignancy in association with Elidel cream.

(Screen.)

Further information relevant to this point. A systematic review of the epidemiologic studies of the topical calcineurin inhibitors was undertaken by Tennis everything al. and published earlier this year in the British Journal of Dermatology. The cutoff date for the review was April 2010. It involved studies in a variety of populations, although these are predominantly studies in adults.

The conclusions of the authors are: that there is no evidence suggesting an increased risk of lymphomas overall or specific subtypes of lymphoma in association with Elidel cream. Furthermore, there's no evidence indicating that melanoma or non-

melanoma skin cancer is associated with Elidel cream.

In an additional case control study specifically addressing the association of lymphoma with Elidel, using data from the PharMetrics database, again there was no evidence of increased risk of lymphoma overall or subtypes of lymphoma in association with Elidel cream.

In late 2010, a clinical study of some 2,400 infants was reported. This was a five-year multi-center open-label randomized study to evaluate short and long-term safety of Elidel cream in these infants with mild to moderate atopic dermatitis. The overall conclusions of this study again is that there's no association of malignancy with the use of Elidel cream.

Lastly on this slide, in late 2009 the FDA requested of Novartis that data from all non-clinical and clinical studies be assessed. That assessment was submitted to the FDA for their review and on completion of the review in July 2010 the FDA communicated to Novartis that the labeling of Elidel was sufficient.

(Screen.)

In 2006, Novartis established an independent global data safety monitoring board with the intent of review of the overall safety profile of Elidel cream. This body meets twice a year and it reviews data relevant to the safety profile of Elidel. This includes study-specific DSMB summary reports for any ongoing studies. It includes MedWatch forms on malignancies and other

clinically relevant SAEs that are reported to Novartis, a pooled analysis of all adverse incidents and serious adverse events from completed clinical studies, and any post-marketing data that may be available.

As of the time of their most recent meeting, which was in late January of this year, the DSMB concluded that, on the basis of information provided from 2007 to 2010 -- and this is actually cumulative information, so it includes information prior to 2007 -- there were no indications of increased risk of development of cancers following the use of Elidel cream. There is no specific pattern of certain types of cancers developing, especially lymphoma and including cutaneous T-cell lymphoma, and there's no pattern of lymphoproliferation short of malignancy.

(Screen.)

There is also an ongoing registry study to evaluate the incidence of cancers in association -- the association of cancers with Elidel use. This is the Pediatric Eczema Elective Registry, which is a study that was agreed with the FDA. It's a prospective ten-year observational registry of pediatric patients ages 2 to 17 with atopic dermatitis who have used Elidel cream.

The SEER database will provide comparator data for the incidence of systemic malignancies that are observed in the general population. Indeed, the principle investigator of the PEER study, Dr. David Margolis of the University of Pennsylvania, is with us here today and can address specific questions with

regard to the PEER study.

The study was initiated in 2004. It is expected to enroll 8,000 patients with ten years of follow-up of each of the patients. As of late March of this year, there are about 5800 patients enrolled and this represents about 17,000 patient years of follow-up to date.

The study-specific data safety monitoring board for the PEER study has reported at its most recent meeting there were no safety findings to date.

So in conclusion, Elidel cream fulfills a medical need in those patients for whom it is indicated. A variety of studies suggest no increased risk of malignancies overall or risk of lymphoma or non-melanoma skin cancer in association with Elidel cream. The benefit-risk profile of Elidel cream is favorable in the approved population. The current prescribing information, including the medication guide, adequately reflects the known safety profile of Elidel cream.

Thank you for your attention.

CHAIRMAN ROSENTHAL: Thank you.

Let's hold questions. We'll have a little bit of time for questions after the presentation from Astellas.

So is there a representative -- oh, coming to the microphone. Thank you very much. Please introduce yourself when you get up there.

PRESENTATION FOR ASTELLAS PHARMA

GLOBAL DEVELOPMENT, INC.

DR. RICO: Good morning, Dr. Rosenthal and members of the committee. Thank you for the opportunity to present today. My name is Joyce Rico. I am a member of the Medical Affairs Department at Astellas Pharma Global Development. I am also a dermatologist.

In the audience with us today is Dr. Peter Heald. Dr. Heald is an emeritus professor of dermatology at Yale. He is a member of the data safety monitoring board for the long-term safety study which Astellas is conducting. He is also an expert in cutaneous T-cell lymphoma.

(Screen.)

I wanted to also begin by talking a little bit about atopic dermatitis. I remember last year the committee had asked some questions about this disease and the issue of why do we care and why do we need to treat it. As a reminder, this is an intensely itchy, relapsing skin disease which currently affects up to 20 percent of school aged children. There are a number of comorbidities associated with this disease, which include an increased risk for cutaneous infections, some of which is due to the persistent scratching that the children and adults with this disease experience. There's a higher rate of asthma, hay fever, conjunctivitis. In patients who have moderate to severe atopic dermatitis, there's a significant impact on the quality of life. This is a life-altering inflammatory skin disease.

(Screen.)

The treatment options for atopic dermatitis are depicted on this slide, and they include as first line therapy topical steroids. Topical steroids come in a variety of classes, ranging from relatively mild up to more potent agents. Those agents, particularly the fluorinated steroids, we prefer to avoid on thin-skinned areas because -- of the face, particularly because of the potential for absorption and hypothalamic pituitary axis suppression.

As second line treatments we have two topical calcineurin inhibitors. Pimecrolimus, Elidel cream, which you've just heard from my colleague, is indicated for those patients who have mild to moderate atopic dermatitis. But for patients who have moderate to severe atopic dermatitis, the approved second line treatment is tacrolimus ointment, or Protopic.

If those patients fail to respond or in the days, which I remember, before we had this agent, those patients would often go on to be treated with either phototherapy or systemic immunosuppressants, including oral cyclosporin, methotrexate, Imuran, and Cellcept.

(Screen.)

This is a patient also presenting with an eczematous disease. It's very itchy. It's widespread, and it looks very much like atopic dermatitis. It is, however, not atopic dermatitis. This is a patient who has cutaneous T-cell lymphoma.

This is a rare T-cell malignancy of skin-homing lymphocytes. It has a presentation that mimics cutaneous -- atopic dermatitis, and is often misdiagnosed as eczema, particularly early in its manifestations.

As this disease progresses, patients develop very widespread disease and it is severe, and it is recalcitrant to therapy. So they're prolonged -- likely to be using a fairly significant amount of topical agents in trying to control it, which will come up in the context of gram usage of product.

MF, which is another name for this, is the most common form of this disease. Skin biopsies are often performed, but they may not be diagnostic early on, and it often will take multiple skin biopsies over years to ascertain the correct diagnosis.

(Screen.)

So putting together cutaneous T-cell lymphoma and dermatitis, it's important to acknowledge that adults particularly who present with chronic recalcitrant eczematous dermatitis are at an increased risk for ultimately being diagnosed with cutaneous T-cell lymphoma.

The mean time from the onset of symptoms to the diagnosis of CTCL, or mycosis fungoides, in at least two studies ranged from 6 years to 15 years. So in other words, these patients have a chronic indolent course and it's going to be very difficult to understand what the true diagnosis is.

Symptomatic treatment is often used because these

patients do have tremendous symptoms and they are itchy. It may include topical steroids, but in those patients, again, who are recalcitrant, they may go on to a topical calcineurin inhibitors, and because they have moderate to severe disease Protopic may be used.

Symptomatic treatment does not alter the disease course, but neither is there data that it exacerbates the underlying disease.

(Screen.)

I want to turn to the reviews that were provided to you as a part of the preparation for this meeting, and the summary from the FDA in the May 10 addendum notes that "The study results suggest the possibility of an association between topical tacrolimus and an increased risk of T-cell lymphoma. However, causality is difficult to determine in light of the potential study biases." Some of that is the information I have just conveyed to you.

We struggle around issues of misclassification. The diagnostic codes and ICD-9 codes for dermatitis are fairly nonspecific. Protopathic bias can also be a contributor, where the pharmaceutical agent, i.e., a topical calcineurin inhibitor, is being prescribed for an early manifestation of a disease that has not yet been diagnosed, CTCL. And there may also be confounding by indication, where the indication for treatment, i.e., a patient who has severe eczema, may be related to the risk

for the diagnosis of the T-cell lymphoma.

I want to note on here also that the callout is on T-cell lymphomas and put that in context with the known literature around immunosuppressants. If you look at the immunosuppressants in data, what you'll notice is that the T-cell lymphoma signal is not the signal we typically see in immunosuppressed patients or animals. Tacrolimus is neither a mutagen nor a carcinogen. In the animal studies that had been conducted with Protopic, animals who are exposed daily for two years do have high exposure, an exposure that's 26-fold higher than the human dose, and there are lymphomas that were observed. But all of the lymphomas or a majority of the lymphomas that you see are B-cell lymphomas. That's consistent with the data we know from transplant, where in transplant recipients who are treated with multiple immunosuppressive agents we know that there's an increased risk for a lymphoma. It's a post-transplant lymphoproliferative disease that is B-cell and also EBV-associated.

What are the risk factors for when patients do develop B-cell or lymphoproliferative disease? The risk factors include the intensity and the duration of immunosuppression. What do we know about the exposure in patients who are treated with topical calcineurin inhibitors? In patients who are treated with Protopic, from the clinical development program we know that systemic exposure in patients with atopic dermatitis is low. Patients who were treated with 0.3 percent who had atopic dermatitis, over 90

percent of them did not have a detectable blood level, and that was at 0.5 nanograms per mill.

When blood levels are detected in patients who have atopic dermatitis treated with Protopic, the blood levels are low, they are transient, and they occur early in the treatment, i.e., they are not sustained.

We have talked -- or we have seen in the FDA materials a statement that in children we are particularly concerned about exposure because of their high BSA relevant to their body weight, and we acknowledge that in some dermatologic applied products that does occur. However, in Protopic there is no increase in tacrolimus blood levels in adults versus children or children versus adults.

In long-term studies, the average use of product daily was .6 to 2.4 grams per day. That's about a quarter to half a teaspoon full. And we know that patients actually used this product intermittently. There's no evidence from the clinical development program of systemic immunosuppression or impaired immune responses in patients who are treated with Protopic.

(Screen.)

We know this drug is effective. This is a child in our pediatric development program who was treated with 0.03 percent Protopic. You can see on the left this child at baseline, with extensive disease involving the head and neck area. At one week, treated only with Protopic, you can see his clinical result in the

middle picture. And finally, at the end of treatment, week 12, you see the child with almost complete resolution of his eczema.

The clinical development program for Protopic has included over 27,000 patients, 9,000 of them pediatric patients. This drug has been demonstrated in these studies to be more effective than vehicle, which was the U.S. development program, as well as in the European studies it was more effective than mid to low-potency steroids and as effective as higher potency steroids, with improvement from baseline, a decrease in the percent of body surface area affected and disease burden, improvement in the eczema area severity index in the individual signs and symptoms of eczema, including itch, improving the time to relapse, and improving the overall quality of life for these patients.

(Screen.)

In conclusion, Astellas recognizes that Protopic is very effective for treating moderate to severe atopic dermatitis as a second-line agent with the caveats as already described. Our analysis of the observational studies and discussions with epidemiologists, with experts in cutaneous T-cell lymphoma, and with those who work in transplant and oncology is that the observational studies that are going to be reported and commented on later today really support an association between patients who present with a chronic dermatitis and a diagnosis of a T-cell lymphoma, particularly mycosis fungoides.

We do not agree that that association can be teased out

that tacrolimus is itself associated with that linkage. Bias, misclassification, and confounders limit the ability to interpret some of these epidemiologic studies that will be described.

Although a causal relationship has not been established, the current product labeling for Protopic informs prescribers and patients and caregivers on the potential risk of malignancy, specifically skin and lymphoma, including cutaneous T-cell lymphoma.

Astellas is committed to continuing to assess the safety of our product, including the completion of the long-term prospective registry in pediatric atopic dermatitis subjects that is ongoing.

I thank you for your attention.

CHAIRMAN ROSENTHAL: Thank you, Dr. Rico.

Let's open the floor at this point for questions and discussion directed specifically at Astellas, at our representatives from Astellas and Novartis who are here. Then I'm going to suggest that we break for lunch and then come back after lunch and hear the agency's presentations.

DR. MURPHY: Geof, since we sort of were able to catch up a little bit, it might be good if we went ahead and did Amy Weitach, because she gives the background for those people on the committee who have never heard any of this, to put it in context for the presentations we just heard. So we might want to do that before lunch since we have sort of caught up, if that's okay with

everybody.

CHAIRMAN ROSENTHAL: That's okay. Let's take a few minutes, though, for our industry representatives, and then we'll do Amy's presentation.

So, questions from the committee? Yes, Dr. Shwayder?

DR. SHWAYDER: I'll start in and, in the spirit of full disclosure, I need to tell my colleagues that both these companies have paid me to give dinners, Novartis a decade ago and Astellas more than a year ago, and both of those have been stopped, as well as my hospital making them illegal.

But I use this medicine, not on a weekly, but on a daily or an hourly basis. I have ten years worth of experience using it on all sorts of diseases. So I'd be happy to answer your questions if it comes up as a practicing dermatologist.

Just to echo what Dr. Rico said, I see mainly children, 80, 90 percent children. In the few adults that I see in the MF clinic, I will tell you 100 percent of them were diagnosed as eczema coming in by some outside person. So it's a very, very common thing for MF to show up being diagnosed as a dermatitis, especially coded, because if you're going to code it before you biopsy it you don't know if it's cutaneous T-cell lymphoma and therefore there's generic codes you use to get it through the system from Blue Cross and the dermatitis one is the easiest one to use. So if you're mining that data, it's very easy to see how this signal comes up.

I'll save the rest of my comments until after everything else goes by.

CHAIRMAN ROSENTHAL: Yes, Dr. Wagener?

DR. WAGENER: I'd actually like to ask Tor a question, and that is: When you're talking about cutaneous T-cell lymphoma, is systemic immunosuppression somehow related to the development of that disease? There was sort of an implication that that might be the case.

DR. SHWAYDER: Well, I'm far from expert and I think there's someone in the room who is. But my understanding is no; it just comes de novo. But I think the gentleman from Yale is here and probably can answer that question.

CHAIRMAN ROSENTHAL: So if you come to the microphone, please just introduce yourself and then we'd appreciate your comments.

DR. HEALD: Peter Heald from Yale University.

I would say probably the best biologic experiment is post-transplant lymphomas, of which CTCL is not part of that cadre, so not traditionally also associated with, say, lupus patients with immunosuppression, where a PTLD has also been reported. So from that signal line, at least CTCL is not regarded as being an opportunistic lymphoma. Also not really found in the HIV population, either. So, regarded as having different risk factors, but not calcineurin or immunosuppression-induced approach.

CHAIRMAN ROSENTHAL: Yes, Dr. Wagener, please.

DR. WAGENER: Is there an animal model for it?

DR. HEALD: There is not.

CHAIRMAN ROSENTHAL: Dr. Rakowsky?

DR. RAKOWSKY: So the majority of the mycosis fungoides patients, do they have a history of eczema to begin with or is it just a misdiagnosed eczema?

DR. HEALD: As Dr. Shwayder was pointing out, they carry a diagnosis of dermatitis. Now, to an academic dermatologist such as myself, there are criteria for making diagnosis of atopic. So even though someone may be referred in with a history of atopic or what's being called in the field as atopic, those patients wouldn't necessarily pass muster as far as meeting criteria for AD. But yes, they would be dermatitic.

So I would say most come in with a diagnosis, as was mentioned, dermatitis. And we do have a code. There's also dermatitis NOS, which is frequently used.

DR. WAGENER: So is there any literature on severe eczematous patients who are started on systemic immunosuppressants, let's say methotrexate for example or retuxemap, where they would actually have a predisposition towards cutaneous T-cell --

DR. HEALD: I would say the model, which is in probably one of your other disease sets, which is the source of several MedWatch reports and publications, is in patients diagnosed with

psoriasis who really do not have psoriasis, but are yet treated with an anti-TNF agent. In that setting, most of the reports that have been published are that the disease accelerates. The ones that we've seen in referral, it appears that the disease accelerates. It's gone from being a thin itchy chronic rash to more of a nodular tumor-type one. Those have been reported with anti-TNF type immunosuppression. But that's a case of mistaken diagnosis, psoriasis thought to have been present, but really B lymphoma. But it just shows you how that disease can mimic both eczema and psoriasis.

That's the only one that's kind of along the lines you're talking about. That is, a patient with rashy skin gets an immunosuppression and then the disease progresses. Typically, if a patient has an eczematous rash they're even treated with immunosuppressants. The menu that was mentioned there for patients who fail that therapeutics algorithm that Dr. Rico had up there: methophenylate, oral cyclosporin, those are all on the menu of managing chronic dermatitis.

CHAIRMAN ROSENTHAL: Thank you.

Other questions or comments?

(No response.)

CHAIRMAN ROSENTHAL: Dr. Shwayder, anything else?

DR. SHWAYDER: I'll wait until the industry. I'd love to see the data and see whether the signals are real or smoke.

CHAIRMAN ROSENTHAL: Thank you for that segue. Then

we'll just move along with Dr. Woitach's presentation of background and updated -- background and update on FDA regulatory and safety reviews of topical calcineurin inhibitors.

Dr. Woitach is a medical officer in the Division of Dermatology and Dental Products.

BACKGROUND AND UPDATE ON FDA REGULATORY AND
SAFETY REVIEWS OF TOPICAL CALCINEURIC INHIBITORS:
ELIDEL (PIMECROLIMUS) AND PROTOPIC (TACROLIMUS)

(Screen.)

DR. WOITACH: Good afternoon, I should say. My name is Dr. Amy Woitach. I'm a medical officer in the Division of Dermatology and Dental Products at the FDA. I'll be providing you with the regulatory background for topical calcineurin inhibitors.

There are two FDA-approved topical calcineurin inhibitors. Tacrolimus ointment was the first product approved in December of 2000. It is indicated for the treatment of moderate to severe atopic dermatitis in non-immunocompromised patients over the age of two. It is available in two strengths. Only the lower strength is approved for use in children 2 to 15 years of age. It is labeled for short-term and intermittent long-term therapy when conventional therapy is ineffective or inadvisable.

Pimecrolimus cream 1 percent was approved a year later in December 2001. It is indicated for mild to moderate atopic dermatitis. Like tacrolimus, it is indicated in non-immunocompromised patients over the age of two and is to be used

for short-term and intermittent long-term second-line therapy only.

At the time of approval, long-term safety for topical calcineurin inhibitors had not been fully established. Animal studies had suggested -- animal studies had been associated with malignancies and the agency requested long-term pediatric registries for both topical products as a post-marketing commitment.

(Screen.)

Subsequent to approval, three Pediatric Advisory Committees have been held. The first was in October 2003 and this addressed the design of long-term safety studies. The second Pediatric Advisory Committee, held in February of 2005, looked at available post-marketing safety information. This committee recommended labeling revisions. These included the addition of a boxed warning and revisions to note second line therapy as well as a means to communicate these changes.

(Screen.)

I will now discuss the labeling of both topical calcineurin products as it applies to safety risk for malignancy.

I will begin with the boxed warning. Again, it is one of the labeling safety changes that was recommended in 2005 by the Pediatric Advisory Committee.

The warning was added to both labels in 2006. Its intent is to inform that the safety has not been established for

long-term continuous use and in patients under two years of age.

(Screen.)

The boxed warning for pimecrolimus is shown here. It does not imply causality. It informs that rare cases of skin and lymphoma malignancies have been reported. It advises against long-term continuous use, excessive unnecessary use, and use in patients under two years of age.

(Screen.)

The boxed warning for tacrolimus is shown here. As you can see, it is similar to the pimecrolimus warning. However, it has the additional warning that only the lower 0.03 percent strength is indicated for children under -- for children to 15 years of age.

(Screen.)

In 2006, additional language was also added to the warnings section, as is shown here. This section warns of infection, lymphoma, and skin malignancies reported in animals and with the use of systemic calcineurin inhibitors in transplant patients. The label advises against use in immunocompromised patients and states that safety has not been established beyond one year of non-continuous use.

(Screen.)

Other labeled safety risks include a statement to avoid use on malignant or pre-malignant skin lesions in the general precautions section. Additional information regarding management

of lymphadenopathy is also included.

Reported adverse events, including lymphoma, basal cell carcinoma, malignant melanoma, and squamous cell carcinoma, were added to the post-marketing sections of both labels.

(Screen.)

Furthermore, a medication guide was issued for both products. The relevant section of the medication guide for calcineurin inhibitors is shown here. It is intended to inform parents and patients of cases of reported lymphoma and skin malignancies and again to warn against long-term continuous use, excess unnecessary use, and use in children under two years of age.

(Screen.)

The third Pediatric Committee was held last year on March 22nd. The committee was presented a five-year update of post-marketing data which included a review of pediatric use data.

This is a slide from last year's presentation, which shows a decrease in the total number of dispensed prescriptions from the year 2005 to the year 2009.

(Screen.)

Also presented at the March 22nd PAC was an update on both pediatric registries and a review of post-marketing adverse event reports of malignancies and infections.

The 2010 committee requested that the agency review literature pertaining to topical calcineurin inhibitors and

malignancy. This will be the major focus of the agency's presentation today.

In conclusion, labeling changes, including a boxed warning, were made to both topical calcineurin inhibitors in 2006.

Based on post-marketing information to date -- this is information which was presented at the 2010 PAC and will be updated for you today -- we have determined that the current labeling is adequate to inform potential safety risks for these products.

Furthermore, following our review of the literature, which we will present next, we have determined that labeling for both TCIs remains adequate.

Any questions?

CHAIRMAN ROSENTHAL: So let's take a few minutes for questions for Dr. Woitach. Dr. Wagener?

DR. WAGENER: A brief question. If I was a patient who was being prescribed this medication, where could I go or how would I go to get some patient-simple information about it?

DR. WOITACH: That's the goal of the MedGuide. It describes it in language that parents and the patients should be able to understand.

DR. WAGENER: And other than the small bit that you showed us there, is it a one-page?

DR. WOITACH: It's a full guide. I just highlighted the section related to --

DR. WAGENER: I wasn't sure if it's something that's ten pages long or one page long.

DR. WOITACH: I believe it's a few pages, one or two.

CHAIRMAN ROSENTHAL: Other questions? Yes, Dr. Shwayder?

DR. SHWAYDER: I'm really curious about what level triggers a boxed warning, because the first sentence -- I have trouble getting my arms around the first sentence. There's no causality, yet we're warning you. I'm at the level of drilling for oil in Alaska causing tsunamis in Japan. Are we going to stop drilling for Alaska?

DR. SHWAYDER: To answer your question, it takes many, many minutes to get the parents over this, and then usually sabotaged by the pharmacist, who says: You know your kid's going to get cancer if you use this medicine. So that answers your question.

Yes, Dr. Murphy?

CHAIRMAN ROSENTHAL: Dr. Murphy?

DR. MURPHY: We are in a very peculiar situation, because we basically are not here to redo what the committee previously did. What was left a little bit out of this is that what happened is that in the first meeting on this there was a lot of work with NIH and the animal model. These were primates. These weren't rodents. And there was a linear association. So let me -- I'm trying to summarize a day's worth of meeting.

Up to 100 percent, okay, of lymphomas in primates.

DR. SHWAYDER: This was the rhesus monkey?

DR. MURPHY: I don't know which primate it was, but it was a primate.

This plus other information, plus the adverse event review at the time, which did have a few cases which were -- again, no one is saying direct causality. On top of which we had a huge amount of use that was off label, okay.

The committee recommended a change to say, we don't know, but we know -- and actually the animal model information, which I fought hard to get in there, was taken out, because I think people need to know. Like you're saying, what's the basis of this. At least that was one of the considerations.

So we did have a statement in the box that says, based on animal model, which is very unusual for a black box, because that was your question. But it can occur. You don't have to have human data.

So this was based on both the animal model and the few cases which no one could make a direct, because of all the things we've already sort of alluded to here.

What the committee said at that time was: You know, we're concerned enough, again because of a very large off-label use and these animal models and the few cases, that we think we should tell people, if you're going to use it, just use it as labeled, use it in these conditions, in this age group, for this

amount of time. And to get that message across, they put in a box.

And there was a lot of discussion and a lot of negotiation that went on for over a year on this topic. At that time, before the labeling negotiations, the committee also said: We want to know just a couple of things. One is we want to know that the off-label use has gone down. So we want you, FDA, to come back to us and show us that the off-label use has gone down. And two, we just want an update on the adverse events.

So that is what we thought was our goal, was to show whether this labeling had any impact or not. You've seen the slide that says it did. And that mostly the committee was focusing in on the under-two year old. That's what they said -- or five. I can't remember. I think it was under two: that we want to make sure that, it wasn't studied, it's not being used, because we did have one high level, and I don't remember which product it was with, of absorption in a child at the immunosuppressive level.

So they said: We just want to make sure that the use has gone down and we want an update on where we are on adverse event reporting. So we did that, and at that time there also was a question about some new information in the literature. And that's sort of where we are now.

We actually gave you the reviews from that meeting and what the recommendations were. But the committee felt, because of

the concerns that were brought up about the literature, that we needed to bring back to the committee not only the reviews that were given to them then, but also a better literature review.

So that's what we're trying to do today, is to say, in view of the previous adverse event review, which fundamentally says we don't think we can make any more causality than we could before, is there anything else in the literature that would change that opinion? And that's what we hope to do for you today.

But it really was not to prepare you to go back and look at all the animal models and go back and rediscuss the whole thing again. Just so you'll know, that's not an uncommon question. Sometimes people on the committee say: I don't agree with the original studies, I don't think you should have approved this product. But to do that, we need to prepare you differently.

So today we're asking you to look at those previous reviews and see if you agree with the conclusions of that review and whether -- if you agree with the presentation on whether we found anything in the literature or not.

CHAIRMAN ROSENTHAL: I'll just affirm -- I'll just affirm that that was the deal that the committee had with the agency. So that is our task today.

Other questions for Dr. Woitach? Other comments? Dr. Shwayder?

DR. SHWAYDER: Why age two? Why age two? Why not below -- I know my colleagues from England use it from zero on up. I've

used it from zero on up. I mean, why age two?

DR. MURPHY: The division may have to help me here, but my understanding back then was this was when people were certain about that diagnosis; and two, that's what it was studied in.

DR. SHWAYDER: But didn't Novartis do a study from three months up, available at the original time?

DR. WOITACH: They've provided one recently.

DR. SHWAYDER: I didn't hear you.

DR. WOITACH: They provided one recently from three months to age two years of age.

DR. SHWAYDER: I thought that had been out for years.

DR. MURPHY: No.

DR. SHWAYDER: No? Okay.

CHAIRMAN ROSENTHAL: The general approach would be to use the information that's available at the time of a decision like that.

You know, I'm wondering, because there are a number of members on the committee who are relatively new, I wonder whether you can speak or whether someone can speak to the general concepts around black box warnings, when are they considered, when are they used, when might the committee see them, when might the committee consider applying them, just in terms of general principles, before we break for lunch.

DR. McMAHON: I think probably a couple of us might want to tackle that a little bit. But -- my name is Ann McMahon. I'm

in the Division of Pharmacovigilance. The considerations around which part of the label the events that we're concerned about go in include benefit-risk, include the seriousness of the adverse events, include maybe even sub-groups in which you're seeing the adverse events and how concerned you are about them.

There's not one formula, though, that -- for if you have X number of adverse events, then you'll do Y. That's not the case. So as I say, it does include the kinds of considerations that I've mentioned. But I'd like to invite others to add to that.

DR. OLSON: My name is Tatiana Olson and I am Deputy Division Director for the Division of Dermatology and Dental Products.

It really depends on the discussion of all available data, and I think standards are changing and today's standards would be different from what it was five years ago. As Dianne already mentioned, animal studies are very rarely being put in a boxed warning. By today's standards, we are required to -- well, sometimes it's not possible to establish causality, but you need to have some causal association between the drug and this particular adverse event. Usually it should be the serious adverse events. It doesn't -- sometimes it's not dependent on the number of adverse events, but just on the seriousness of the adverse events. But it's a subjective decision made by the individual divisions.

CHAIRMAN ROSENTHAL: Dr. Rakowsky?

DR. RAKOWSKY: Just a follow-up on the question Dr. Wagener had. If you have a black box warning, so medication guides aren't found with all prescriptions -- if you have a black box warning, is that an automatic trigger to have a medication guide included for the patients?

DR. OLSON: Yes.

DR. MURPHY: We'll get the specific language before we come back from lunch. But I think what people are trying to tell you is it has to be serious. It's something you want people to think about, so it has to be serious, usually. It does not have to be definitively linked, okay. As I said, it's rare to have it based on animal data, but it can happen. So I think those are the three sort of concepts.

CHAIRMAN ROSENTHAL: Yes, Dr. Romero?

DR. ROMERO: I had a question not related to the black box warning. But looking at this from my little silo of the world, which is infectious diseases, these T-cell lymphomas are not related to HTLV-1? These are independent, non-HTLV-1-associated T-cell lymphomas?

CHAIRMAN ROSENTHAL: Dr. Rico, you're standing up. Would you like to come to the microphone and help us answer this question?

DR. RICO: Dr. Heald has just walked out of the room and we could ask him when he comes back. But yes, we acknowledge that

there are peripheral T-cell lymphomas that are HTLV-1. But cutaneous T-cell lymphoma in this context, mycosis fungoides, is not.

CHAIRMAN ROSENTHAL: Thank you.

Any other comments before we break for lunch?

(No response.)

CHAIRMAN ROSENTHAL: Okay. Well, we have a lot to think about at lunch, but not a lot to talk about at lunch.

(Laughter.)

CHAIRMAN ROSENTHAL: So please refrain.

DR. MURPHY: I got your black box warning. Well, first of all, it's not black. So it says: "Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data." As I said, we felt we had a little bit of both.

"The box must contain upper-case" -- and it goes on to describe upper case letters, "a heading inside the box includes the word 'Warning' and conveys the general focus of the information in the box. It must briefly describe the risk and refer to more detailed information in the contraindications or warnings and precautions section, accompanied by the identifying number."

So I think we gave you about as much as you're going to get on that.

CHAIRMAN ROSENTHAL: Excellent. Thank you. Thank you very much.

So again, let's break for lunch now. Please refrain from discussions of the matters at hand in your lunch meetings. We will start exactly -- we will start at 1:30. That's when we'll have the open public forum. That's the one anchor in our meeting.

So we can move other things around at times, but that we can't. So we'll see everybody at 1:30, and enjoy your lunch.

(Whereupon, at 12:31 p.m., the meeting was recessed, to reconvene at 1:29 p.m. the same day.)

AFTERNOON SESSION

CHAIRMAN ROSENTHAL: It is now 1:30 and in keeping with our approach for the day of being exactly punctual, we'll go ahead and get started.

(Pause.)

CHAIRMAN ROSENTHAL: Before we get started, I'd like to take a moment and have Doctors Notterman and Santana please introduce yourselves. Thank you for joining us. We're glad you're here for the afternoon session. Either one of you can go first.

DR. NOTTERMAN: I'm Daniel Notterman. I'm Vice Dean and Professor of Pediatrics, Biochemistry, and Molecular Biology at Penn State.

DR. SANTANA: I'm Victor Santana, a pediatric hematologist-oncologist, presently at St. Jude's Children's Hospital in Memphis, Tennessee.

OPEN PUBLIC MEETING

CHAIRMAN ROSENTHAL: Thank you.

This is the point in our meeting where we're open for a public hearing, and there's 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 decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes

that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with 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 such financial -- if you have no 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.

We have one speaker, but before we do that I'll just let people know, the members of the committee and the public, that periodically the agency receives email and other communications from people in the public who would like their comments to be acknowledged in this setting. There are times when the intent and the content of these comments are not clear to me as the Chair and, rather than go through them in great detail, I try and summarize them.

Today we received -- or for this meeting we received an electronic communication. I'll just -- this one I'm just going to read to people so there is a sense for some of the information that comes in, some of the comments that come in. But it's regarding this meeting. It says:

"Something desperately wrong here. Not enough protection for the kids. The committee seems to be a pimp for the drug industry and certainly not enough involved in protecting American kids. I find that appalling. The American public wants more protection for our kids. The dosage of 70 doses" -- that's 7-0 -- "doses of vaccine is harmful. It is an assault on their bodies."

That's the end of that statement.

So we have one person signed up to provide a statement at the open public forum. Dr. Lawrence Eichenfield, if you can please come to the mike. Yes, just to the mike at the center of the room, please.

REMARKS OF LAWRENCE EICHENFIELD, M.D.:

TOPICAL CALCINEURIN INHIBITOR (TCI) AND CHILDREN

DR. EICHENFIELD: Thank you so much. There are some slides.

(Screen.)

Good afternoon. Thank you for allowing me to speak. I'm Lawrence Eichenfield. I'm Chief of Pediatric and Adolescent

Dermatology and Professor of Clinical Pediatrics and Medicine at Rady Children's Hospital, San Diego, and University of California-San Diego. I'm a pediatrician, dermatologist, and pediatric dermatologist, and I'm Co-Director of the Eczema Center in San Diego.

I appreciate the opportunity to speak today. I have no conflict of interest to disclose at the present time. I have in the past been an investigator for these drugs, but have no business or consulting relationship with either Astellas or Novartis.

If we can have the next slide.

(Screen.)

I really want to discuss atopic dermatitis in children. On behalf of the Society for Pediatric Dermatology and the American Academy of Dermatology, we wanted to start off by saying that we greatly appreciate the work of this committee and the FDA and its advisers in trying to balance safety and efficacy of drugs. We also wanted the committee to understand how atopic dermatitis has significant impact in our children throughout the United States. In fact, new information in our understanding of atopic dermatitis pushes us to change some of our therapeutics regimens of care.

So, for instance, there's been a tremendous evolution in understanding pathogenesis of atopic dermatitis. We now recognize

that there are a significant number of genetic defects, such as thallogren mutations, that cause inherent barrier dysfunction in atopic dermatitis, and this is sort of pushing us to stress early effective management of atopic dermatitis.

There is a limited armamentarium of FDA-approved medications for management, especially long-term management, of pediatric atopic dermatitis. We'd like to request the reconsideration of the application of the black box warning for the topical calcineurin inhibitors.

Next slide.

(Screen.)

Atopic dermatitis is a high prevalence disease. The United States figures estimate a prevalence of 17 percent of children with atopic dermatitis. It manifests with severe skin barrier dysfunction, eczematous rashes, pruritus, secondary infections; and also secondary effects that impact on the individual and the family, such as significant sleep disturbance, school and job performance impact.

Atopic dermatitis, while predominantly a disease of children, can continue on until later childhood, with less than half having complete resolution by age 7 and a significant persistence into adulthood.

Next slide.

(Screen.)

The economic burden in the United States has been

estimated at \$3.8 billion a year, and there's increasing evidence that atopic dermatitis is sort of an entryway into other atopic diseases. And there have been several longitudinal studies in the last decade that have restated in very well-controlled studies that atopic manifestations generally will begin with atopic dermatitis, but that the comorbidities are very high, with an incidence of asthma developing in atopic dermatitis-affected individuals at the rate of 11 to 50 percent, food allergy in 15 to 40 percent, variably dependent upon the severity of atopic dermatitis, and allergic rhinitis in 25 to 75 percent of patients.

Next slide.

(Screen.)

Emollients and corticosteroids are the most common treatments for atopic dermatitis. Few emollients and corticosteroids specifically have FDA approval for the atopic dermatitis indication and fewer for very young age.

The treatment specifically of moderate to severe atopic dermatitis with systemic and topical corticosteroids can involve risks and adverse events that are greater than or equal to that of the topical calcineurin inhibitors. These include growth retardation, organ-specific side effects, and skin atrophy.

Next slide.

(Screen.)

The TCIs pimecrolimus and tacrolimus are not new drugs. They've been used for over ten years and extensively evaluated in

the management of pediatric atopic dermatitis. They are in fact the most well studied topical products for pediatric dermatologic use nationally and internationally of any drug that we use in dermatology, with an unprecedented number of infants, children, and adults enrolled in large, prospective, international, multi-center, short and long-term clinical studies; has an excellent safety profile and database of use. The studies show utility and safety both in short-term use and long-term intermittent use in maintenance therapy.

(Screen.)

The black box warning itself has had a significant impact, has generated tremendous negative attention, fear, and emotional trauma for families whose children have used TCIs or families who are considering the use of TCIs in the management of atopic dermatitis. It's also impacted our other therapies. There is some evidence of an apparent increased use of systemic corticosteroids as the management of individuals with AD with moderate to severe persistent or frequently flaring AD. It has also negatively impacted research studies. There were several long-term studies that were discontinued after the placement of the black box warning, and it's had impact in general on pediatric drug development for atopic dermatitis in children.

(Screen.)

So how safe are the TCIs and how can you balance the risks? A tenet of dermatology training is that you have to look

at side effects of topical agents in relationship to systemic absorption and systemic effects. That is, that the topical safety profile, the safety profile -- an agent that's administered topically may not be the same as that if it's used systemically. The blood levels in AD patients are much, much lower than oral levels and there has been no adverse effects on the immune system that have been observed in children with TCI use. Neither systemic immunosuppression nor in provocative studies such as vaccine studies and T-cell immune studies has there been evidence of an impact.

In the five years since the labeling, there's been no compelling evidence of a causal link of TCIs with malignancy in children.

(Screen.)

We have seen some data and we'll see some data in the next presentations listing malignancies, and we just ask that it be looked at in clinical context. You have to look at the frequency of malignancies in children in general, and also remember when you look at children in the United States, if 17 percent of them have atopic dermatitis, it would be expected that in this population there would be malignancies that develop.

We remember that what was being -- the greatest concern initially with these drugs from a systemic absorption standpoint is whether we would see the sort of malignancies that we're seeing with systemic use of some of the calcineurin inhibitors. That is,

that the malignancies we'd be seeing would be non-melanoma skin cancers or post-transplant lymphoproliferative disease. And there's been no evidence of that to date.

(Screen.)

The other clinical context has already been brought up by several people this morning, but I'll speak as a pediatric dermatologist to the issue of cutaneous T-cell lymphoma. The data is similar in pediatric CTCL, that this is a disease that generally presents with either localized or broad-based scaly eczematous plaques, of long duration from onset to diagnosis. In a recent series just published last year, 2.4 years from the onset of rash until the diagnosis cutaneous T-cell lymphoma.

Therefore, many pediatric patients get treated both with topical corticosteroids and with TCIs prior to the appropriate diagnosis.

We know that there's a limited knowledge as to how the disease state itself influences malignancy. We can see in some of the data that's reviewed in epidemiologic studies that there may be a higher relative risk to atopic dermatitis in terms of its association with malignancy independent of therapy. It's unknown if severity influences this, and we have not had evidence of skin cancer emergence in the pediatric atopic dermatitis population with these drugs.

(Screen.)

We have our registries, APPLES and "Pears," or "PEERS,"

as the case may be, and we've seen that data presented by both of the companies -- 6100 children, which they've been followed for over five years; and 5791 patients enrolled. The registries support large epidemiologic and MedWatch studies with the lack of a malignancy signal.

Next slide.

(Screen.)

So the American Academy of Dermatology Association and the Society for Pediatric Dermatology encourage the FDA to reconsider the application of the black box warning, understanding that there's a significant unmet need for pediatric dermatology care in this population and that the removal of the black box may allow more appropriate treatment of children with moderate to severe AD.

I thank you for your time.

CHAIRMAN ROSENTHAL: Thank you, Dr. Eichenfield.

Let's move forward in the -- are there other speakers for the open public forum?

(No response.)

CHAIRMAN ROSENTHAL: Okay. The open public session is adjourned and we'll move forward with our meeting.

So for the next presentation from the FDA, the current literature review of topical calcineurin inhibitors Elidel and Protopic will be given by Dr. Manthripragada. Dr. Manthripragada is an epidemiologist in the Division of Epidemiology in the Office

of Surveillance and Epidemiology in the FDA's Center for Drug Evaluation and Research.

CURRENT LITERATURE REVIEW OF
TOPICAL CALCINEURIN INHIBITORS:

ELIDEL (PIMECROLIMUS) AND PROTOPIC (TACROLIMUS)

DR. MANTHRIPRAGADA: Good afternoon. Again, my name is Angelika Manthripragada. I'm from the Office of Surveillance in Division of Epidemiology at the FDA.

Today I'll be presenting results of the literature review we conducted on topical calcineurin inhibitors, or TCIs, and malignancies in pediatric patients.

(Screen.)

The objective of this literature review is to determine whether published observational studies suggest an increased risk of malignancies among pediatric patients using TCIs. We conducted this review in response to a request by the Pediatric Advisory Committee.

The presentation is divided into two sections. I'll begin by going over the results in summary of the skin and other cancer study findings, and then go over the results in summary for the lymphoma studies.

(Screen.)

We used a stated search criteria and identified five observational studies published between January 2005 to April 2011. We also included a study submitted to the FDA by one of the

drug sponsors. Of the six reviewed studies, four evaluated lymphoma risk, one evaluated non-melanoma skin cancer risks, one evaluated melanoma skin cancer risk, and one studied other cancers.

(Screen.)

Five of the six reviewed studies were funded by Novartis and the remaining study by Queen was funded by Kaiser Permanente.

(Screen.)

This table provides an overview of the reviewed studies evaluating the risks of skin and other cancers among pimecrolimus, or PIM, and topical tacrolimus, or TAC, users. The Hui study evaluated report risk of melanoma and a number of other cancers listed in footnote number 3. The retrospective cohort study used a Kaiser Permanente northern and southern California database and associated Kaiser cancer registry to identify cancer cases. Exposure was captured using prescription data. The study employed a 6 and 24-month lag period. A lag period is defined as a time period after initial drug exposure during which person, time, and outcome events are not counted.

The Margolis study was a case-controlled study conducted at the U. Penn. Dermatology Department. This study used a questionnaire to determine TCI exposure and their own dermatologic database to capture non-melanoma skin cancer data. No lag period was employed in this study, meaning events occurring immediately after drug exposure would be attributed to the exposure.

(Screen.)

This table includes a brief description of additional aspects of both studies. The Hui retrospective cohort study included patients with atopic dermatitis or eczema diagnosis for patients of all ages. The Margolis case-controlled study used a broader inclusion criteria of dermatitis and only included those 30 years of age or older. I have also listed for your reference the total sample size, the pediatric sample size, and follow-up times when available.

(Screen.)

In this slide we present hazard ratios for the Hui cohort study and odds ratios for the Margolis case-controlled study. Results did not suggest an increased risk of melanoma or non-melanoma skin cancers in TCI users. No association was reported for any of the other studied cancers.

(Screen.)

As previously stated, we only found two published observational studies examining association between TCI use and skin and other cancers. These studies had several limitations. First, both studies were of relatively short duration, given the outcome of cancer. Furthermore, there is little information specific to the pediatric population. Although the Hui study included pediatric patients, it didn't perform any analysis stratifying by age. The non-melanoma skin cancer study by Margolis didn't include any children.

Lastly, the potential for misclassification is a limitation. Hui did not perform a medical record review of cases and Margolis used self-reported exposure data as well as some self-reported diagnosis information.

(Screen.)

I will now move on to discuss the lymphoma studies. We reviewed two cohort and four nested case controlled studies. However, it's important to note that the Arana 2010 study is actually an extension of the Arellano 2007 study, meaning it includes all the data in the Arellano 2007 study plus an additional four years of data.

All included studies were U.S.-based, with the Hui study being limited to the state of California. We excluded one U.K.-based study. No analyses of TCI use were performed in this study since TCI use recorded in this database were very low.

Study periods ranged from 1995 to 2009. Studies included time periods prior to TCI approval and do so to evaluate topical corticosteroid use. All studies used prescription data to capture the exposure.

The Hui 2009 study used a cancer registry to identify cases. Besides capturing outcomes using the Kaiser Permanente cancer registry, they also reviewed exposed T-cell lymphoma cases using medical records to ascertain exposure time in relationship to disease outcome.

Schneeweiss used ICD-9 codes followed by chart review

for case validation, while the remaining two studies used only ICD-9 codes to identify cases.

Hui, Schneeweiss, and Arana looked at subtypes of lymphoma, whereas Arellano looked only at overall lymphoma risk.

The last column gives the lag times which were used in both studies. Hui and Schneeweiss both incorporated a 6-month lag time in main analysis, whereas the remaining studies used no lag time for their primary analyses. Hui also performed sensitivity analyses using a 24-month lag time and Arana performed a sensitivity analysis using a 6-month lag time.

(Screen.)

All studies used other atopic dermatitis patients as a comparator group and required six months of continuous enrollment in the selected database. Schneeweiss, Arellano, and Arana excluded individuals with a history of cancer, immunosuppression, transplantation, and anti-cancer therapy, since these individuals are at a higher risk of cancer. Hui et al. only excluded those with previous history of cancer, but later controlled for some of the other exclusion factors in their analyses.

The total sample size, the pediatric sample size, and follow times are included on this slide for your reference.

(Screen.)

I will now present the study results by type of lymphoma. This table summarizes study results for any lymphoma. Although the Schneeweiss cohort study reported elevated risk

ratios, the 95 percent confidence intervals included the null.

The two case controlled studies, Arellano and Arana, did not report any associations. Arana also looked specifically at individuals under 20 years of age and found no association with TAC or PIM and lymphoma.

(Screen.)

The Schneeweiss study nested case controlled analysis and the Arana study also evaluated the relationship between cumulative TAC or PIM use, duration of use, and the risk of lymphoma. Higher PIM use was associated with a fourfold increased risk of lymphoma compared to lower topical corticosteroid use. Lower levels of PIM use also showed elevated odds ratios. However, the 95 percent confidence intervals included the null.

Cumulative PIM use showed no association with lymphoma in the Arana 2010 study. However, this study did not report -- did report an association between higher cumulative TAC use and risk of any lymphoma. No association was reported in either study with increased duration of use.

Two studies looked specifically at T-cell lymphoma and both reported an increased risk among TAC users. Hui reported a threefold increased risk of T-cell lymphoma, while Arana reported a near fivefold increased risk. Neither study reported an increased risk of T-cell lymphoma among PIM users.

(Screen.)

Results of analyses evaluating cumulative use and T-cell

lymphoma in the Arana study showed odds ratios of increasing magnitude for increasing cumulative exposure compared to non-use.

The study reported a sixfold increased risk of T-cell lymphoma in TAC users with greater or equal to 06 to less than .1 gram, while TAC users with greater than or equal to .1 gram showed an approximately twelvefold increased risk of T-cell lymphoma. There were no associations reported for PIM. Confidence intervals are wide, reflecting the small sample size in most exposure groups.

(Screen.)

This slide describes the T-cell lymphoma cases identified in the Hui study. 16 out of 100 T-cell lymphoma cases were exposed to a TCI. In 4 of the TCI-exposed cases, chart review showed that the treating physician believed that the patient had cutaneous T-cell lymphoma before exposure. These cases were excluded from further analyses.

Median time from TCI exposure to diagnosis was 1.4 years for TAC and 1.7 years for PIM users. There was one exposed pediatric patient. This patient was exposed to TAC and then to PIM.

(Screen.)

This slide describes the T-cell lymphoma cases identified in the Arana study. 6 cases were exposed to PIM, 14 to TAC, and 2 were exposed to both TAC and PIM. 117 of the 118 cases included skin involvement. The mean time from first drug exposure to diagnosis of any type of lymphoma, not necessarily T-cell

lymphoma, was 1.87 years for TAC and 2.06 years for PIM. Details specific to the pediatric T-cell lymphoma cases were not given.

(Screen.)

These studies evaluated the risk of B-cell lymphoma in TCI users. Hui reported elevated hazard ratios among PIM users, although the 95 percent confidence intervals included the null. Elevated hazard ratios were not noted among TAC users. The Arana study sample size is too small to draw any conclusions.

(Screen.)

Two studies evaluated the risk of Hodgkin's and non-Hodgkin's lymphoma among TCI users. Neither study reported an association with Hodgkin's lymphoma. The Arana study noted an increased risk of non-Hodgkin's lymphoma in TAC users. Schneeweiss did not report an association between either TCI and non-Hodgkin's lymphoma. This is the same -- the previous study was the same study that reported an increased risk of T-cell lymphoma. lymphoma.

In summary, there is no evidence of an association between TCIs and B-cell lymphoma. However, there were very few published observational studies to review. The only study to evaluate the risk of B-cell lymphoma found a small, non-significantly increased risk. However, this study only adjusted for age and sex in their analyses and did not account for the use of other immunosuppressants. Also, for these analyses the study did not review charts to determine the relationship between timing

of exposure and outcome.

There is evidence suggesting an association between TAC use and an increased risk of T-cell lymphoma. The two studies evaluating this potential association both reported a large increased risk for any TAC use compared to non-using atopic dermatitis patients. The study evaluating cumulative dose suggested an increased risk of T-cell lymphoma with increasing cumulative use of TAC. However, we cannot be sure that the reported associations are causal. There remains the possibility that these associations could be due to biases, such as protopathic bias. Protopathic bias refers to bias that can occur when a drug is prescribed for an early manifestation of a disease that has not yet been clinically detected or diagnosed.

In the reviewed studies, many of these cases were cutaneous lesions, which could be misdiagnosed as atopic dermatitis, prompting a doctor to prescribe a TCI to apply to the lesion. However, the Hui study reported this observed association even when using 6 and 24-month lag periods. Additionally, the Hui study reviewed all exposed cases to determine whether there was any evidence that the lesion existed prior to exposure.

Furthermore, of protopathic bias accounted for these findings one would potentially expect to see an association between PIM and T-cell lymphoma or topical corticosteroid use and T-cell lymphoma, but this was not consistently reported.

(Screen.)

There is not much evidence of an association between PIM and T-cell lymphoma. Two studies show no increased risk in T-cell lymphoma for PIM users. These results are not necessarily inconsistent with the reported associations between TAC users and T-cell lymphoma, since one study does report that TAC has eight times higher T-cell inhibition than PIM. Thus the study suggests that it may be biologically plausible that one could have a greater increased risk of T-cell lymphoma in TAC versus PIM users.

However, results suggesting an association with TAC and not PIM could also indicate that there is confounding by indication, a type of bias that arises from differing baseline risks between patients who receive treatment and those who don't.

TCIs are second-line therapies and non-users are not likely to have as severe atopic dermatitis as users. PIM is used for mild to moderate atopic dermatitis and thus may be more similar to the control group with regard to baseline or prognostic factors than TAC, which is used for moderate to severe atopic dermatitis.

Although some studies did control for disease severity, there is a possibility of residual confounding.

(Screen.)

Analyses looking only at lymphomas as a group may miss a true association since grouping all lymphomas together could mask individual lymphoma risk. The Arellano study only looked at all lymphomas, which could explain why they didn't notice an increased

risk. Furthermore, power of the studies decreased when studies evaluated lymphoma subtypes. For example, the Arana study didn't have enough power to discern differences in B-cell lymphoma.

(Screen.)

Misclassification of disease status is also a problem in these studies. Arana and Arellano relied on ICD-9 codes to capture and sub-type cancer diagnoses. Using this information, Arana could only categorize about 60 percent of their cases into sub-types.

Another limitation is that studies cannot capture long-term effects, given the follow-up time. The mean follow time was approximately two years, which is not long, given the outcome of cancer. Furthermore, the studies may have limited generalizability for children. Although the studies did include children, there was no stratification by pediatric age groups and few to no details on individual pediatric cases.

(Screen.)

In conclusion, our review of the observational literature suggests a possible association between TCI use, particularly TAC, and an increased risk of T-cell lymphoma. However, potential study biases, including protopathic bias, confounding by indication, and misclassification, could in part account for these findings.

Study results also need to be considered in light of the following. The review study results pertain to both adults and

children as a group. We had limited to no data on children only.

Also, these studies were of relatively short duration, given the long latency of most cancer outcomes. These studies also were generally quite small, especially for looking at sub-types of lymphoma. Lastly, there were few studies examining associations between TCI use and B-cell lymphoma, melanoma, and non-melanoma. We cannot draw any conclusion regarding these outcomes with such limited data.

Thank you.

CHAIRMAN ROSENTHAL: Thank you.

Let's now move to the presentation by Dr. Namita Kothary on post-marketing AERS cases of pediatric malignancies reported with topical calcineurin inhibitors. I'd also like to just say for the record, Dr. Notterman, we're very glad you're here. We've sort of combined the discussions on Protopic and Elidel. You are recused from the vote, but we'd appreciate your comments.

UPDATE ON POST-MARKETING AERS CASES OF
PEDIATRIC MALIGNANCIES REPORTED WITH TOPICAL
PIMCROLIMUS AND TACROLIMUS USE

DR. KOTHARY: Thank you. Again, my name is Nomita Kothary and I'm a safety evaluator in the Division of Pharmacovigilance I in the Office of Surveillance and Epidemiology.

Today I'll present an update on pediatric malignancies in the FDA's adverse event reporting system database that were reported with the use of topical calcineurin inhibitors, pimecrolimus and topical tacrolimus. This is an update to information presented at the Pediatric Advisory Committee in March of last year.

(Screen.)

I will begin by providing background on previous postmarketing safety reviews of pediatric malignancies in AERS, followed by the objective of this presentation. Then I will describe the inclusion criteria for the pediatric malignancy case series and summarize results of the AERS search. Finally, I will provide conclusions and then open the discussion up to the committee.

(Screen.)

Cases of pediatric malignancy as reported with TCI use have been described in previous post-marketing safety reviews and presented to the PAC on multiple occasions, as described in an earlier presentation. The most recent PAC, in March 2010, discussed the 56 cases of pediatric malignancies shown in the last two lines. The summary shown later in this presentation will account for these cases.

(Screen.)

As mentioned on the previous slide, pediatric malignancies reported with the use of TCIs have been presented to

the PAC on multiple occasions. However, we continue to receive new cases and follow up information from previously identified cases. Therefore the objective of this presentation is to provide an update of pediatric malignancy cases in AERS reported with TCI use, including a summary of the new cases and updated total case counts. (Screen.)

Before describing the methods and results of this update, I want to take a moment to describe the FDA AERS database. AERS is a voluntary spontaneous adverse event reporting system designed to detect signals for adverse events possibly associated with marketed drugs. Its strengths include detecting rare or unexpected adverse events, especially those not seen in clinical trials, in which the study populations may be limited. However, the AERS database has a number of limitations, including underreporting, variable quality and quantity of information provided, and may be subject to factors affecting spontaneous reporting, such as media, regulatory actions, and how long a drug is on the market. Additionally, AERS is not the optimal tool for adverse events with a long latency period, such as malignancies.

(Screen.)

Moving into the methods, we searched the AERS database to identify cases of pediatric malignancies. Since we continue to receive follow-up information that may change the classification of previously captured cases, we searched for reports received by the FDA since market approval of both products.

Additionally, in order to retrieve cases that did not report a specific age from zero to 16 years, but did report that the adverse event occurred in a child or pediatric patient, we did not limit the search by age. Therefore we searched adverse event on March 4, 2011, for cases of pediatric malignancies associated with pimecrolimus and topical tacrolimus. We then analyzed the cases based on the reported adverse event terms, as well as information provided in the case narratives. We included cases in children zero to 16 years old or cases that indicated that the adverse event occurred in a child, infant, pediatric patient, etcetera. The case also had to report a malignancy or cancer, an uncontrolled growth of cells that resulted in lack of differentiation, local tissue invasion, or metastasis, or the cases had to report brain tumors or other tumors affecting the central nervous system.

We excluded cases in adults or where we could not determine the age. We also excluded cases that reported benign, non-malignant or unspecified tumors or neoplasms, or cases that reported pre-malignant conditions. And we also excluded cases that did not report a definitive diagnosis of a malignancy.

(Screen.)

Based on the case definition described in the previous slide, we identified 72 unduplicated AERS cases of pediatric malignancies reported with TCI use. 43 of these reported the use of pimecrolimus. 22 reported the use of topical tacrolimus and 7

cases reported the use of both products. 15 of the 72 cases were new. However, only 4 of these were reported to the FDA after the March 2010 PAC meeting. The remaining 11 cases were reported to the FDA prior to the March 2010 PAC meeting and were retrieved in this search because they contained null values in the AERS age field.

The remaining 57 cases were captured in previous AERS reviews and have already been presented to the PAC.

(Screen.)

In order to provide the PAC with up to date totals, this figure shows the current AERS case counts of pediatric malignancies reported with TCI use by quarter. This figure accounts for both new malignancy cases, shown in black, and follow-up information received for previously captured cases, shown in grey. As mentioned on the previous slide, some of the new cases were reported prior to the last PAC meeting and were captured because they reported null values in the AERS age field.

As described earlier, a boxed warning containing information regarding potential risks for malignancies was added to both product labels in January 2006. In the 2 years and 9 months prior to the boxed warning, we received 17 cases. In the 5 years and 3 months after the boxed warning, we received 55 cases.

(Screen.)

This slide provides a high-level summary of the total pediatric malignancy cases, separated by the cases that were

previously captured and reported to the PAC and the new cases that have not been reported to the PAC as yet, or that I'm reporting now. Lymphomas and leukemias remain the most commonly reported pediatric malignancies, both in the new cases as well as overall.

The next four slides go into more depth regarding the specific malignancies.

(Screen.)

We received four new cases of lymphomas: one case each of B-cell lymphoma, Hodgkin's disease, cutaneous T-cell lymphoma, and an unspecified non-Hodgkin's lymphoma. Overall, the cases did not provide sufficient detail to assess the clinical course of events. Therefore no new trends were identified for the lymphomas.

(Screen.)

We received six new cases of leukemias. Five cases reported ALL and one case reported an unspecified leukemia. ALL accounts for the most commonly reported pediatric malignancies in the 15 new cases. This is consistent with the previous AERS reviews, in which ALL was the most commonly reported pediatric malignancy.

(Screen.)

Although we identified two new cases of skin malignancies, we have insufficient information to classify these cases at the present time. The case of melanoma may be a duplicate of a melanoma case described in a previous AERS review.

However, we don't have sufficient information to reconcile these two cases.

Additionally, follow-up information is pending for the case that reported an unspecified skin cancer.

(Screen.)

We received three new cases of other pediatric malignancies: one case each of rhabdomyosarcoma, neuroblastoma, and pituitary microadenoma. However, based on the limited number of cases and the lack of sufficient detail, no new trends were identified.

Overall, the pediatric malignancies we identified are consistent with those described in previous AERS reviews. We did not identify any new trends based on the new cases. Taking into account the new malignancies identified in this review, as well as malignancies identified in the prior AERS reviews, these cases support the previously identified potential safety signal for malignancies reported with TCI use. However, the precise role that the TCIs play in the development of malignancies is unknown.

In general, the information provided in spontaneous post-marketing case reports is not sufficient to determine causality. In the majority of the new cases, information regarding the clinical course of events, details regarding drug exposure and the role of underlying diseases, as well as other contributing factors, were unknown. Additionally, malignancies may be associated with a long latency period, making it difficult

to attribute the adverse events to a drug.

(Screen.)

This slide summarizes our overall conclusions based on the FDA reviews. The review of observational literature suggests a possible association between TCI use, particularly topical tacrolimus, and an increased risk of T-cell lymphoma in all ages combined. However, potential study biases remain a possible explanation for this observed association. Additionally, the results were not specific to the pediatric population.

Based on the new pediatric malignancy cases in AERS discussed in this presentation, we did not identify new signals for pediatric malignancies reported with TCI use. Therefore, the agency feels that the current TCI labeling and medication guide reflect the safety risk as we understand it.

(Screen.)

Based on our conclusions, we ask the PAC today if you agree with the following recommendations by FDA: One, FDA will continue routine surveillance of spontaneous reports and continue to monitor for registry cases; and two, the Protopic and Elidel labels and medication guides adequately reflect the risk for malignancies.

Thank you.

CHAIRMAN ROSENTHAL: Thank you very much.

So we've got time for some discussion on these points.

Yes, Dr. Santana?

DR. SANTANA: I have a question that kind of may lead into a comment. I'm more interested -- and I apologize that maybe this was discussed this morning, and if it has been just tell me and I'll shut up. But I'm more interested in terms of beginning to understand the potential power of the prospective registries, because I think, as you and the previous FDA presenter have adequately addressed, there's a lot of limitations with the retrospective data and a lot of limitations with the AERS.

So I'm confident that if the registries are built correctly that they will help answer some of the issues that we've been facing in the past and we face today. So can you tell me in terms of the registries what data is being collected on the patients that are registered and, more specifically, on the patients that develop malignancies, what specific data is collected on those patients?

DR. KOTHARY: I think I'll defer this to the division, who follows the registries.

CHAIRMAN ROSENTHAL: Thank you for coming up to the table, and if you can please just introduce yourself when you come up.

DR. WOITACH: My name is Amy Weitach. I'm a Medical Officer in the Division of Dermatology and Dental Products.

There are two registries. The one for Protopic is -- well, both registries are to be 8,000 subjects followed for 10 years. The Protopic registry is collecting data on both

infections and malignancies and the Elidel registry is looking at malignancies.

DR. SANTANA: More specifically, are they looking at usage of drug over a period of time?

DR. WOITACH: Yes, they are collecting information on --

DR. SANTANA: Are they looking at conditions that may predispose these patients to develop malignancies, like if they've had a pre-cancerous syndrome or condition or something like that? Do you know?

DR. WOITACH: I'm not sure if that's --

DR. SANTANA: And when there's a malignancy reported, is there, particularly in the lymphomas and leukemias, is there detail, a phenotype of those malignancies, so we can try to answer back the associations between these and other immunosuppressants?

DR. WOITACH: I'm not sure of the detail.

CHAIRMAN ROSENTHAL: Dr. Rico, would you like to address the question?

DR. RICO: Yes, thank you. The APPLES program, which was initiated in 2005, has currently 6500 patients enrolled. The patients are predominantly contacted by phone every 6 months with individuals who are trained to solicit information. That includes whether the patients have seen a health care provider. We're specifically looking in detail for information around skin biopsies, other biopsies, or hospitalizations.

For every SAE that is identified, we have a safety group

that goes back to get additional information and that information is provided to the agency in the context of both our periodic safety update reports and also in our study. We have an independent end point review committee composed of three pathologists with expertise in dermatology and oncology. They review the materials as they are provided to us in order to independently ascertain whether that is a patient with a malignancy. We have a scientific advisory committee that's international, with expertise in epidemiology and in -- actually, the person who leads the children's oncology group, Tom Gross, who's an expert in transplant malignancies, is a member of that committee. Then finally, we have a data safety monitoring board.

So these three committees, which are independent, are actually working to help us both with the design elements and also to ascertain that as we see the events coming in whether we have a signal.

Our most recent data is that in the numbers of malignancies that we have seen we do not have a signal. The study does work, because we have been able to identify malignancies in the population of children.

DR. MURPHY: Could we have you tell the committee, because I may have been told this and I don't have it -- now, you've told us how many are going to be enrolled, 8,000, and you've got 6,000 enrolled so far?

DR. RICO: Over 6,500.

DR. MURPHY: Then how -- what's your projection for getting the ten years? In other words, from your first patient supposedly you'll have ten years; what would that be?

DR. RICO: Well, those numbers changed dramatically, as you saw before, when the product use changed in 2006. I would have to ask our statistician to help me in looking at that. But we do have somewhere around 12,000, 14,000 patient years, and we'll continue to accrue.

The study was powered based on the 8,000 patients in ten years and based on the underlying rates. I'll point out that they're based on the SEER rates, which are coming from a general healthy patient population. As we talked about this morning, we might argue that the rates for patients who have atopic dermatitis or are diagnosed with atopic dermatitis may not be the same as in the general population. But, that being said, we think that we're adequate to address that issue, particularly as it relates to lymphomas and malignancies.

CHAIRMAN ROSENTHAL: Thank you.

Other questions for Dr. Rico, and then I'll ask Dr. Goldstein for his question.

(No response.)

CHAIRMAN ROSENTHAL: Okay. Dr. Goldstein.

DR. GOLDSTEIN: So I am feeling that we're feeling different parts of the elephant. On the one hand, we have information that there's a hazard signal in some small, relatively

small studies, with not a good -- with no denominator and incomplete data. On the other hand, we have a larger database that's suggesting that there's actually no signal, but the trick is to try and disprove a negative.

So I'm wondering how the dermatologists from Yale and San Diego and representing the ADA and the pediatric dermatology group reconcile this, the different messages that we're getting, and if you have an answer for this conflict for us.

DR. HEALD: Well, thank you again for the opportunity. Again, my expertise is with cutaneous T-cell lymphoma, and I think when you talk about the observational studies having a signal, the signal that's in there is that patients with a chronic relapsing pruritic eruption are at high risk for having a diagnosis of T-cell lymphoma in their future. That part is pretty much standard practice.

So the signal isn't so much the agent. It's more that amino phenotype. However, you then look at, as our second presenter did a little while ago, differences between pimecrolimus and tacrolimus, and the differences there are really on-label. So the way that I reconcile that is that patients with moderate to severe disease tend to get the moderate to severe drug.

So a patient with a chronic relapsing dermatitis, especially the adults who are in these studies that you're talking about, the observational studies, those are ones more likely to be treated with tacrolimus versus pimecrolimus. Now, if you were to

ask me, can you prove that, I would say it's been proven. It's in that Hui study. Those patients with moderate to severe chronic dermatitis were exposed to tacrolimus. Not that many had both and not that many were pimecrolimus with that.

So I think we're talking about the signal of this very frustrating disease, and for those pediatricians on the board who are not familiar with the fact that when we mention lymphoma we're really talking about these observational studies, mycosis fungoides. So we're not talking about young kids with big lymph nodes. We're talking about these adults with this itchy rash eruption. And people with that setting, that moderate to severe itchy, rash eruption, yes, they're at greater risk of both being treated with non-topical steroids because those have failed, and of having a diagnosis of T-cell lymphoma in their future.

The last point I'd leave you with, which I don't think I made clear earlier, is in the few studies that have been done, just because it's so expensive, going backwards, once you make a diagnosis of T-cell lymphoma in one of these folks, several groups have published going backwards, going back to their biopsy from eight years ago. Now that we have a patient-specific primer -- and actually they had clonal disease back then, when you could not diagnose it.

So the current model that most lymphoma people agree to is, this is actually a disease from day one. The mycosis fungoides does not spring out of a hotbed of chronic dermatitis,

but it actually is a chronic dermatitic eruption from early on that just eventually announces itself.

CHAIRMAN ROSENTHAL: Thank you.

Dr. Rakowsky actually had a follow-up question for Dr. Rico and we skipped him. I'm sorry.

DR. RAKOWSKY: In the APPLE study, you're following down the road 8,000 patients for up to 10 years. What's the exposure to drugs that they're getting during those 10 years? Is it chronic exposure for the whole time?

DR. RICO: Right. That's a great question. We do capture what drugs patients are receiving, and we were recognizing in particular that some patients, for example the tacrolimus-treated patients, had prior exposure to cyclosporin and to other agents because they do have really bad eczema. We continue to follow those and we will continue to look at them. We also ask them about their current product use.

I can't get those numbers to you right today, but we do keep that as a part of it. The idea behind that and the design, which was done in conjunction with Annette Stemhagen, a well-known pharmaco-epidemiologist, was to be able at the end of the day look at product exposure. If you think the product is associated with a disease state, i.e., a malignancy, then would we be able to differentiate those patients who had low exposure versus high exposure?

Product drug is very, very difficult, and I've been with

the company since the days of these original clinical trials. Even when you hand someone a tube and you get them to come back and you weigh the tube, it's still very difficult data to get a good handle on. But we are tracking.

DR. RAKOWSKY: Is there some bare minimum of the product that they have to be on?

DR. RICO: Both for our study and for the Novartis-conducted study -- and I hesitate to speak for my colleagues -- every patient must have had at least six weeks of treatment prior to enrolling. What's interesting about our study is that we've looked at these patients; they are coming in with years' worth of exposure. We are counting the days from the time they actually enroll in the study so that actually we do know about both, both from what their prior use was as well as their use going forward.

CHAIRMAN ROSENTHAL: Thank you.

Dr. Notterman, we'd like to hear your questions and comments. I'm wondering if you can try and keep them focused on Elidel.

DR. NOTTERMAN: I think my questions about extended accruals has been answered.

CHAIRMAN ROSENTHAL: Thank you.

Yes, Dr. Shwayder?

DR. SHWAYDER: I'm fascinated by the differences between tacrolimus and pimecrolimus in the registry, because they both have the same mechanism of action. They're slightly different

molecules, the penetration's about the same. One's an ointment and one's a cream. And this break between moderate to severe to light to moderate, I don't see that in the real world. It has more to do with whether you're willing to use an ointment versus a cream.

Most of the pictures I saw this morning which they're calling bad eczema, that's nothing compared to the stuff that walks into my office on a daily basis. So I would have called that mild.

So I think that it's a false division. But I'm fascinated because the APPLES and the PEERS or the two different drugs will have the data ten years from now, and I guess only the generics will profit by it. But I still want to see the data.

CHAIRMAN ROSENTHAL: Other questions?

(No response.)

CHAIRMAN ROSENTHAL: Any discussion on the medication guides and labels for these? Yes, Dr. Shwayder?

DR. SHWAYDER: I guess I have to ask a question of the FDA. You know, we'll have 20 years data when we have 20 years data. What needs to happen to take off a warning, as a generic question?

DR. GOLDSTEIN: This is related.

CHAIRMAN ROSENTHAL: Okay, Dr. Goldstein has a related question.

DR. GOLDSTEIN: My related question is, what are the

unintended consequences of a boxed warning and how does that affect whether you take it off or not? Which is -- one of the things that struck me was the increased use of steroids after the boxed warning came out, which may not be such a good thing.

CHAIRMAN ROSENTHAL: So just to be clear, I want to make sure that everybody recognizes that we're not here to decide whether or not the boxed warning should be changed per se or removed per se. That's not a question that we've been asked. We've been asked whether we think the label and medication guides adequately reflect the risk of malignancies. So we'll try to focus on that.

DR. SHWAYDER: That doesn't answer the question. I'd be curious, because it's generic to all drugs. Once you put it on the label, you're stuck forever.

DR. GOLDSTEIN: Are you putting a little bit too fine of a point on that? Because there's a consensus, at least from two on this side of the table.

DR. SHWAYDER: I'm sorry, I didn't use the microphone. My question was: It's generic to all drugs. Once you put it on the label, what do you have to do to get the label off?

DR. MURPHY: Basically, the standard answer is sort of like: Show me, show me the data. That's the bottom line. You don't -- the box is to say this is what we know now. We have a concern because of all of the reasons already stated.

We didn't set up this meeting to go through all of those

reasons again. And we set up a process to look at, as we said, was there an impact on the population that hadn't been studied and a population that was off-label in the use, and to continue to monitor and to continue to see what comes in from these studies that are set up.

I think when we have enough data that would say, despite the animal models, because that's a hurdle you have to overcome, and maybe with new data that comes in with cancer and being able to have some of these earlier biopsies that you could follow over time, you would get to a level of more certainty that there was not a risk, because one of the things that Dr. McMahon brought up is that we're always looking at risk-benefit here, and we know this is a serious disease. I've been called in to see some of these kids, too.

So it's in the context of do we have enough data to say we're now comfortable that we've raised this question, that we can answer it. So in a way, yes, it's easier to tell people to be careful than it is to say, now we know you don't need to.

CHAIRMAN ROSENTHAL: Dr. Rogol.

DR. ROGOL: Well, I'm not so good at government-speak. So I am more used to the National Football League, and if you have a play and it is called one way, you have to have convincing evidence that it ought to be overturned. So what I'm asking is, once you have a box on the label, do you have to have clear and convincing evidence to the contrary to overturn the black box --

the box? Excuse me, it's not a black one.

DR. MURPHY: We don't have video, unfortunately.

(Laughter.)

DR. MURPHY: I'm not doing government-speak. What would you call clear? I'm sure there's some people in here that would say they think it's clear and they don't want to wait ten years to get the answer.

DR. ROGOL: Let us vote.

DR. MURPHY: Yes.

The others would say, you know, you haven't provided us the background data. You have not seen the reason the box was put in. So if you think it should be removed, then I would, if I were you, as a scientist say: I'd like you to come and show me the data and let's revisit it, all of it, than to say because we've presented you with a piece of it today that you know all of it.

DR. ROGOL: Fair enough.

CHAIRMAN ROSENTHAL: Dr. Rakowsky?

DR. RAKOWSKY: Having been trained at FDA and having worked there, I know the focus of the label is usually at the product level, so you don't put in there the consequences of a change. So for example, if you put a boxed warning it's really not in the mandate to say what's this boxed warning do to the practice of medicine outside.

Let me throw out a hypothetical question. If there is a study that shows that use of oral steroids actually has increased

threefold in this population, would that change the level of evidence needed to then delete the warning as it is right now? In other words, at what point does level of evidence go higher because you've noticed a change in practice outside?

DR. MURPHY: It would -- Alex, you know that we can't answer that question. We have to put it in the context of what is the full picture. That's all I'm saying. You have to put it in the context of what's the full picture at this point, because we, as I explained this morning, we're on a path here today that we didn't even send you the previous reviews.

So that's why I'm saying, if you feel strongly -- some people do -- that you want to consider removing the black box, then you should vote that we have a session to look at that, because you don't have the data to make that decision today. That's what I'm telling you.

CHAIRMAN ROSENTHAL: Thank you.

Dr. Santana.

DR. SANTANA: So I think these registries are really important, and I don't think we should throw them out today. I think they've accrued over 75 percent of their target, which I think is quite impressive. I'm very impressed that in a four or five-year period the sponsors and the agencies have been working through to diligently get these registries to work. And I know they cost money, I know they influence practice and all of that.

But this is a unique opportunity with this class of

agents to really work through these registries and let the registries go to completion. What you may want to consider -- and I'm not a biostatistician; I was looking to see if Jeff was in the room, and the table -- is to look at, after you've accumulated 100 percent of the registrations and then some period of time, to then begin to mine the data and see if you're getting enough information that would sway you one way or another.

I know you don't do interim monitoring after the horse has left the race track, but you may want to do that. You may want to define and specifically then bring it back to us at that time point, what is the data showing. Rather than taking these peaks and these four cases here and these ten cases there, which I just think confuses the picture even more, let the data speak for itself at one critical point. And maybe at that point you can bring it back to the committee.

That would be my suggestion to the agency. Let the registries accrue, let them accrue 100 percent of the participants, and define now prospectively with the sponsor and the group at the FDA when you want to do the first peak at that data.

CHAIRMAN ROSENTHAL: Dr. Anderson, do you have any comments on Dr. Santana's points?

DR. ANDERSON: I think it's an excellent suggestion to define a monitoring plan for an observational study. It's pretty unique. Mostly it's applied only to clinical trials, but it would

add some very valuable rigor to the analysis of this.

I'd also like to suggest that more be done to mine the HMO databases. I can't believe that they don't already have in their pharmacy databases and in their cancer registries more data that could be brought to bear on this question, much more rapidly than this cohort that's going to have some problems accruing at the same rate that was anticipated.

CHAIRMAN ROSENTHAL: Thank you.

Yes, Dr. Shwayder?

DR. SHWAYDER: On the same lines, to mine more data from the people like my colleague at Yale, if we took ten patients who had tacrolimus and T-cell lymphoma and pulled up their biopsies from before they got tacrolimus and saw that the clone was there, that's a huge indicator on the side that it was a predetermined genetic thing and not swayed by the topical application.

So I guess, can you define those sort of data beforehand, not being a statistician? There are lots of biopsies out there in big medical centers. The Mayo Clinic keeps track of all of them. Can we go and pull them and do them? You can do them on paraffin-embedded tissue as well.

CHAIRMAN ROSENTHAL: So I'm hearing a few things. One, I'm hearing that the label, in general that the label is an organic vehicle for communication, and that the goal, I think everybody's goal, is to have it reflect the best available information, recognizing that that information may be imperfect.

The other thing that I'm hearing is I'm hearing some good ideas for ways to clarify the informational uncertainty that exists in the labels for these TCIs.

Are there other things that people are hearing or that we should be honing in on on this topic? Dr. Reed?

DR. REED: Well, coming back to your original charge about in the portion of the label, the medication guide, does it appear to adequately address this. I was reviewing that during this spirited discussion and as far as I'm concerned it adequately addresses. It states: The link that Elidel cream could cause these cancers has not been shown. It states what one's looking at, but it also I think very clearly states the state of where we are today.

CHAIRMAN ROSENTHAL: Yes, Dr. Neville?

DR. NEVILLE: If I can just echo Dr. Reed's comments, I think data mining are helpful, but we still -- as far as I'm concerned, I don't have the prospective data in my hand to make a definitive decision that causes me to feel comfortable with changing the label.

CHAIRMAN ROSENTHAL: Dr. Wagener?

DR. WAGENER: Just to get back to what the FDA suggested, I also compliment the last two FDA speakers. I thought their presentations were superb, because I entered this with the two questions. One is: Review the literature, and they gave us a review. And two was: Here's the label; do you agree that we

should leave it the way it is?

Now, during the open session the question was thrown out at us should we get rid of a black box warning, which wasn't part of the original challenge. But I must admit going into the first of the last two talks I was sort of thinking that.

But then in the literature review at least one study -- there's limited numbers, but one study -- shows a dose response effect, shows a statistical relationship. And with that, going back and trying to change the label would be crazy. Admittedly, we don't have great data, but what's out there in the literature clearly would not want us to step backwards.

I don't think it's enough to step forwards, but it wouldn't step backwards. So as I see the discussion today, we've seen the literature review. It's consistent with what was chosen by a previous committee to put on the label. We've looked at the label and we agree that, based on the current data from AERS, there is no reason to change it more aggressively, because that was your nice report. And I don't know if -- and now we have some good ideas on what to do prospectively in these large studies, which clearly is going to be what's necessary to prove this, unless somebody comes up with a biologic model that shows one thing or the other.

CHAIRMAN ROSENTHAL: Thank you.

Dr. Towbin and then Dr. Shwayder.

DR. TOWBIN: It appears to me that we have consensus on

one thing, which is that we don't have sufficient data. And I think the passions tend to run high when you don't have scientific information to be able to chew over. I think it would be a mistake to make a decision without allowing the data to speak for itself.

CHAIRMAN ROSENTHAL: Dr. Shwayder.

DR. SHWAYDER: Dr. Kothary, in your presentation I believe you said there were four that showed no association and one that did. Am I remembering that correctly, four studies?

DR. KOTHARY: For the literature? That's actually the EPI review.

DR. SHWAYDER: Dr. Manthripragada. I guess my question is, It's like going to a tumor review board. Four is non-malignant, one's malignant; okay, what do you do next?

I'm trying to remember the powers of the four versus the one, because everyone here is glomming onto the one and maybe that was a CTCL clinic at Yale or something, or Kaiser.

CHAIRMAN ROSENTHAL: Please speak into the mike.

DR. MANTHRIPRAGADA: There were several studies and it depends if you look at overall lymphoma risk or the T-cells. The T-cell, I think also it was the Arana study showed that dose response association, while the Kaiser study showed just an association. So there was more than one study showing a potential association with tacrolimus.

DR. SHWAYDER: But not with pimecrolimus, not with

Elidel.

DR. MANTHRIPRAGADA: No.

DR. SHWAYDER: Explanation, please, Mr. Spock?

DR. MANTHRIPRAGADA: Like we said, there was a study that said that it could potentially -- for T-cell lymphoma, that tacrolimus could have the higher T-cell inhibition, and there was also the potential of confounding by indication.

DR. SHWAYDER: Right. Thank you.

CHAIRMAN ROSENTHAL: Thank you.

Other points of discussion?

(No response.)

CHAIRMAN ROSENTHAL: All right. Well, let's vote on these questions. Thank you, Dr. Notterman.

The first question: Does the committee agree that the FDA should continue surveillance of spontaneous reports and should continue to monitor the registry cases? All in favor of that?

(A show of hands.)

CHAIRMAN ROSENTHAL: I'm sorry. Dr. Shwayder, you're recused from this vote.

DR. SHWAYDER: From half of it.

CHAIRMAN ROSENTHAL: From half of it. Which half?

DR. SHWAYDER: I think from the tacrolimus half, but not from the Elidel.

CHAIRMAN ROSENTHAL: It may be best to -- why don't you refrain from voting right now. I think we understand your

opinions and if you'd like to take a moment to describe them afterwards that would be good.

All right. So the first question pertains to both drugs. Thank you for clarifying, Dr. Towbin. Should the FDA continue surveillance of spontaneous reports and continue to monitor for registry cases for both drugs? All in favor of that?

(A show of hands.)

CHAIRMAN ROSENTHAL: Any opposition?

(No response.)

CHAIRMAN ROSENTHAL: Okay. Dr. Rogol?

DR. MURPHY: Before you get to the second question, I know you need to poll too, but we had a bit of discussion about registry, what you would like. Maybe, Geof, can you try to articulate what you think the committee would like us to do as far as some interim monitoring of the registry?

CHAIRMAN ROSENTHAL: We can do that. But let me just run around the table on this first question.

DR. MURPHY: Yes.

CHAIRMAN ROSENTHAL: Let me just finish that one thing.

DR. ROGOL: Al Rogol. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. MOTIL: Kathleen Motil. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. ANDERSON: Garnet Anderson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. REED: Michael Reed. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. SHWAYDER: Tor Shwayder, recused.

DR. SANTANA: Victor Santana. Yes.

DR. ROMERO: Jose Romero. Yes.

CHAIRMAN ROSENTHAL: Thank you.

Then before we leave this first point, let's take a moment to address Dr. Murphy's recent question. You're asking specifically for some ideas regarding the monitoring of the registry cases?

DR. MURPHY: Yes. The division's telling me, though, that the protocols are set and they can't do anything to change them.

CHAIRMAN ROSENTHAL: Dr. Rico?

DR. RICO: Just a point of clarification. The protocol for APPLES does call for a formal interim analysis.

CHAIRMAN ROSENTHAL: Do you know when that will take place?

DR. RICO: Five years after patients are enrolled.

CHAIRMAN ROSENTHAL: Thank you.

DR. SANTANA: The last patient enrolled? Could you clarify that? The last patient enrolled?

DR. RICO: We have members of our DSMB who might do a better job of that than I do. But the intent was that it would be at approximately halfway through the study.

DR. AFTRING: And I would add, the PEER study has similar features.

CHAIRMAN ROSENTHAL: Would you mind restating your name into the microphone?

DR. AFTRING: Sorry. I'm Paul Aftring from Novartis Pharmaceuticals.

CHAIRMAN ROSENTHAL: Thank you.

DR. MURPHY: I'm sorry. What did you say about your study?

DR. AFTRING: The PEER study has similar features and it calls for an interim analysis.

DR. MURPHY: Okay, I'm sorry. It's a similar feature.

CHAIRMAN ROSENTHAL: Yes, Dr. Anderson?

DR. ANDERSON: So if there's a chance to modify that, it would be a little bit more informative if it were after half the projected number of cases were accrued of lymphoma or whatever cancers we're looking at.

CHAIRMAN ROSENTHAL: Dr. Murphy, does that address your issue? Okay.

Other thoughts about Dr. Murphy's question before we move on to the second question on the slide?

(No response.)

CHAIRMAN ROSENTHAL: Okay. So "Protopic and Elidel labels and medication guides adequately reflect the risk for malignancies." My question is how do people feel about this, given what we know today? All who feel that this is kind of -- so one of the things about the FDA is they like to present us with compound questions. But I'll try and address both Protopic and Elidel and both labels and medication guides all as one lump, and if as you vote and consider these issues we need to split these apart in some way, please just speak up.

But let me ask the question of whether the labels and medication guides for Protopic and Elidel adequately reflect the risk for malignancies? Everybody who believes they do, please raise your hand.

(A show of hands.)

CHAIRMAN ROSENTHAL: Anybody who believes that they don't?

(One hand raised.)

CHAIRMAN ROSENTHAL: I'll give you a chance to articulate your thoughts again after the vote.

All right. So I'm not seeing any -- among the voting members, I'm not seeing any dissenting votes. So let's go around the room. Dr. Romero?

DR. ROMERO: I agree.

DR. SANTANA: Victor Santana. Yes.

DR. NEVILLE: Kathleen Neville. Yes.

DR. REED: Michael Reed. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. ANDERSON: Garnet Anderson. Yes.

DR. TOWBIN: Kenneth Towbin. Yes.

DR. RAKOWSKY: Alex Rakowsky. Yes.

DR. MARTINEZ ROGERS: Norma Martinez Rogers. Agree.

DR. MOTIL: Kathleen Motil. Yes.

DR. WAGENER: Jeff Wagener. Yes.

DR. ROGOL: Al Rogol. Yes.

CHAIRMAN ROSENTHAL: Okay, thank you.

Dr. Shwayder, please. Please articulate your thoughts.

DR. SHWAYDER: My worry is always balancing what's the real risk with the safety of the patient, which is our charge. And I'm worried that they're skewed data and that they're overstating the risk, which is leading to harm in other ways, as Dr. Alex mentioned earlier. And I would just hope that part of our charge to the FDA was to have adequate plans in place so that we could answer these questions and remove the warnings that are unnecessary.

CHAIRMAN ROSENTHAL: Would you like to help us come up with some concrete ways that we can -- at what point -- so the current thinking is that at roughly the halfway point for each of the ongoing registry studies there will be a look and FDA will continue to monitor that. Are there other things that the agency

should do to try and shore up the evidence and help us make this decision in this organic document?

DR. SHWAYDER: Not being a trained statistician, I don't think I can come up with the exact things. I like the idea of mining the biopsy data and then having more clear-cut diagnoses. Part of that is just the nature of the ICD-9 codes, which are very -- in terms of dermatology, there's not enough codes to sub-segment, sub-specialize what we're doing.

The other things that got mentioned this morning I think will get to it. I'm afraid that it provides way too much warning for the indication that's there. But I'm not a voting member.

CHAIRMAN ROSENTHAL: Well, regarding your point, though, I wonder whether other people around the table have other ideas that might help the agency to drill down into some of this data in a way that's expedient? Other thoughts?

DR. SANTANA: We had mentioned a few of them before, but I will reiterate the ones that I think would be of interest. I think if the registry could explore the associations between duration of use and cumulative use; particularly with the lymphoproliferative -- by that I mean lymphoma -- and leukemias, if we could get information about the amino phenotype of those malignancies, just to begin to understand if biologically they're different from the other types of malignancies that we're accustomed to seeing sporadically in kids in general.

I think the idea that was suggested earlier,

particularly with these patients that have skin conditions that have been biopsied, that eventually then go on to develop cutaneous T-cell lymphoma, those are very rare in kids, I'm sure, but if they do occur that we should have adequate information to go back and restudy those from a genotype and a clonal perspective to see if the disease was there from day one or if it's a different disease three years later after using these products.

Then I think I would like to know if any of these patients particularly have any precancerous syndromes that would also predispose them to develop these kind of malignancies, and I'm thinking particularly of Wiskott-Aldrich, where patients can present with eczema and skin manifestations and then they develop hemologic malignancies later on. So that familial pre-cancer syndrome history would be very important.

So those are four suggestions that I would focus on.

CHAIRMAN ROSENTHAL: Thank you.

Dr. Wagener?

DR. WAGENER: This is addressing sort of the second issue that you bring up, and that is the implication that was made earlier that because this drug was not being used as much that other therapies may be used and that those therapies could theoretically have more adverse effects. Comparative efficacy knowledge is reasonably well established in the epidemiology world. It seems like with the huge database that somebody like

Kaiser would have, somebody, with two wealthy drug companies out there wanting this, they could go to that huge database and start to look at that question.

This was a drug that was used quite highly for a period of time. It has lowered utilization now. You've got some good comparison time frames, and within a large standardized data set they should be able to look at other alternative therapies that might be out there.

So I would argue that that's where you ought to be going if you're going to use the argument that without this people are having some other therapy that's more adverse.

CHAIRMAN ROSENTHAL: Dr. Rogol?

DR. ROGOL: One of the things that I would urge you to do -- we're talking about a proper study. We're not talking about let's look at this, let's look at that. Proper studies cost bucks. So if we're going to do it part way, I don't think we ought to do it. But is there an FDA -- that's the question -- is there an FDA or other mechanism other than the drug companies, which is obviously where you would ask, that this kind of proper study could be done and it would be scientifically validated before it was ever started?

Because if you don't get good data, you may as well not do the study.

CHAIRMAN ROSENTHAL: My understanding -- please correct me if I'm wrong -- but my understanding is that the registries

were the industry's response to issues that were raised in previous Pediatric Advisory Committee meetings in response to a request by the agency for additional data to inform this question.

DR. ROGOL: I was actually thinking specifically of pathologists going over the skin biopsies, looking together at some that are six or eight years apart, which could be very informative, especially with immunologic markers. And those are not cheap. But you've got exactly the population you're looking for and you don't need 87,000 patients. You need really very few.

So that's the kind of thing. Focus where you know you'll get an answer. There's statistical power in maybe two dozen patients. I made that number up, but it is a relatively small number compared to all of the other kinds of studies that we have talked about. Perhaps one or more of the statisticians in the group might comment on what I just said.

CHAIRMAN ROSENTHAL: Before we do that, I think one of the IRB chairs in the group might want to comment on what was just said. Dr. Rakowsky had his hand up first.

DR. RAKOWSKY: I may have misheard, but I thought there are three pathologists already looking at all the cases in at least one of the studies. Is that correct, or for both studies? Because that would answer both of your questions, maybe even add onto one.

DR. ROGOL: You're agreeing with what I'm getting at.

DR. SANTANA: I think the suggestion that I hear across

the table is actually you have the registry, you have the database, and at some point you're going to make a decision and you're going to begin to mine it. And the suggestion, which is where I'm coming from, too, is let's define soon what that database mining study is going to look like. What are the questions that we want that database to answer for us? And then bring those questions together so that they can be answered at that point.

Because the data is going to be there. It may be zero, right? Which would be great. But I think the suggestion I think we're having is, as you're getting closer and closer to the point where you're going to look at the data, maybe this is a good opportunity to begin to formulate what are the questions that you want that database to answer.

Whether that's called a study, whether it's called whatever, I'm not into that. But I think that's I think the reflection of the discussion as I understand it from both sides of the table.

DR. OLSON: I just wanted to mention that those registries were designed several years ago and the protocols for both registries deal extensively with cost. And I'm not sure at this point, when both registries are basically more than halfway through, they will be able to answer all the questions that you are raising here today.

DR. ROGOL: If you didn't collect the data, you didn't

collect the data. I agree with you. That's why -- I think that's okay. If you don't have the data, you don't have the data.

DR. OLSON: And you're asking for something more. Probably you need to ask the sponsors whether --

DR. ROGOL: But I think you need to begin to formulate the questions that you want answered from that.

DR. OLSON: I'm just afraid that you're setting up kind of unreasonable expectations here from those databases.

DR. ROGOL: I'm not asking you to do more. I'm not asking the company to do more. I'm not asking people to send more money or more effort. What I'm saying is you have a database and, not knowing what's in the database, this could be an opportunity to begin to pose the questions that you want that database to answer. The answer may be: I don't have the data; the registry wasn't designed to answer that question. That's okay with me. That's not your fault, it's not the sponsor's fault. Maybe it's our fault when we had the discussion five years ago. But that's a different issue.

DR. MURPHY: I think what I'm hearing is what the committee is saying -- and I'm saying this both to the division and the sponsors -- that if you really want to reconsider the way to address whether we can remove the boxed warning, these are the kind of things that need to be considered.

CHAIRMAN ROSENTHAL: Thank you.

Dr. Rakowsky, did you have another?

DR. RAKOWSKY: I guess I'm a little confused. I thought that these registries already have some of those questions answered. Maybe it's just to clarify that you already have some of this data in there. We're not going to be looking at huge amounts of cases, and maybe this adding some retrospective immunostaining to these biopsies isn't all that hard to do. I don't think it rewrites an entire study to add these things in there.

I mean, the way at least -- I looked briefly at these protocols and I think a lot of the questions that we're asking for have already been sort of built into these protocols.

CHAIRMAN ROSENTHAL: Thank you.

Just to clarify, we got off on this path because I asked the committee to come up with just some food for thought, some reflection about ways that we might enhance the information base in making these decisions. So thank you to all of you for your thoughts.

Other points of discussion on the TCIs?

(No response.)

CHAIRMAN ROSENTHAL: All right. I'd like to turn the floor over to Dr. Murphy at this point.

DR. SHWAYDER: Geof, I guess I have one other question. They alluded to several times to off-label use, and I mentioned this morning that every time you have a new hammer everything looks like a nail. Well, there's many mysteries in dermatology

and every time there's a new cream we all use it for it. It wasn't studied for it, so we're using it for vitiligo, using it for lots of things.

I don't know that with data mining -- would the adverse events come out? If we're using it for vitiligo and someone has a side effect, would it be reported? Or is it generic right to eczema? Is everyone keyed into that?

CHAIRMAN ROSENTHAL: Can I just clarify in my own mind. You're reflecting on the discussion that we were having around Lexipro and Intuniv, where we were talking about looking for adverse events across different diagnostic groups and with co-occurrence of other medications?

DR. SHWAYDER: How did that come to the surface? Or did the FDA really hone right in on eczema?

DR. McMAHON: Well, if you're -- are you talking now about asking a question about AERS?

DR. SHWAYDER: Yes.

DR. McMAHON: We do -- we do get reports of off-label use in AERS, if that's what you mean, yes.

DR. SHWAYDER: They're just categorized as non-eczema use? Just they're in AERS?

DR. McMAHON: Well, the reports are sometimes very detailed and sometimes not at all detailed. So we might or might not get a lot about the indication or what have you. But sometimes we will be able to tell a fair amount about how it was

used.

DR. WAGENER: Although just by example, in this one that we just looked at with TCIs, when you queried AERS, you put in an age or child or whatever, you then you also put a diagnosis in of either atopic dermatitis or eczema. I guess that was the literature review, wasn't it, that they did that.

So when you do AERS, do you do the same thing, in which case if you put in a diagnosis you would miss the off-label use? Or you're doing it strictly by drug?

DR. McMAHON: Well, there are different ways that you can mine AERS. You can use text string searches and different things. If you look in just the indication field, you might not see it. But you might see it within the text or something.

CHAIRMAN ROSENTHAL: Actually, before I turn the podium over to Dr. Murphy, I just want to give one more plug. Please return your confidential disks. It's very, very important that this information get back to the agency.

Now, Dr. Murphy.

DR. MURPHY: Yes, they all have little disks. We'll track you down. No. Please, just send them back in.

Clearly, as I said, we need to do a lot of training because of the new members and to address many of the questions that you've -- valid questions about what are the limitations of AERS, what can we do. What can we do with some of these new databases that we have? We do have that on our agenda, to do more

of that with the committee, because the agency does not have access to additional databases.

But I want to thank you all very much. We heard some really I think thoughtful suggestions today. I know it's hard to be recused -- a new action verb.

But Dr. Notterman is the, should we say, the super person for having the most complicated conflict of interest form, which he has heroically filled out as a dean, because now we have this thing that I don't even want to try to describe and I think would drive everybody to drink, which is "imputed conflicts," which has created an enormous path and a long path for all of us to be able to get some of you here to this committee to review.

So I don't want anyone who couldn't vote to feel like they were picked upon. Believe me, we had to argue to get you to the table. I think I would like to have the committee recognize that Walt Ellenberg has spent thousands of hours -- and I am not exaggerating -- getting you to the table here today so that we could show that you could have a discussion and it would be as free of conflict as we could possibly make it. So, Walt, I want to give you my public recognition of the work that's gone into this.

Dr. Notterman, you are going off the committee and in a way I'll have to say we have loved your discussion and we've loved your insight, but you have raised the bar now. We know how to write reviews for conflict of interest being a dean that I don't

think many people do. But we would like to recognize your work and your commitment, and please come up and receive a plaque as you're going off the committee --

(Applause.)

-- for the effort that you have put into coming to this committee and doing all of that paperwork and answering our calls: We need more information about how you're not making decisions about this.

I really do mean it. I think I've never seen anybody work as hard as you and Walt have to make sure that you have the opportunity to provide your insight.

Did you want to say anything since this is your last meeting?

DR. NOTTERMAN: I want to say that it's been a wonderful few years. I've made many friends and gotten to reestablish old friendships.

I have to say that it wasn't that much work for me. In addition to the conflicts that come with being a dean, so does a staff at an office of sponsored programs. But it was a lot of work for them.

CHAIRMAN ROSENTHAL: Dr. Notterman, I'm sorry. I'm going to have to ask you to step away from the podium because of a conflict of interest.

(Laughter.)

DR. NOTTERMAN: Thanks, Dianne.

DR. MURPHY: Thank you very much. We really do appreciate it.

Thank you.

CHAIRMAN ROSENTHAL: All right. All right. Well, the formal meeting is adjourned at this point.

(Whereupon, at 3:02 p.m., the meeting was adjourned.)